ASSESSING THE CURABILITY OF CANCER

by

T. W. LEES.

I N D E X.

TABLE I.

CANCER MORTALITY.

Site	Sex	1901-1910	1911-1920	1921-1930	1938
All sites	M	784	897	1000	1066
	F	942	959	980	961
Lip	M	12.8	12.6	11.4	8.1
	F	0.8	0.7	0.7	0.7
Tongue	M	43.1	50.8	45.9	28.5
	F	4.4	4.3	3.8	3.5
Oesophagus	M	51.2	60.6	64.1	50.8
	F	14.6	16.5	18.0	18.4
Stomach	M	167.2	186.4	220.2	231.6
	F	133.0	139.0	154.2	150.5
Intestine	M	63.5	96.8	124.8	142.8
	F	72.3	109.2	128.5	139.1
Rectum and anus	M	79.8	93.6	105.0	113.7
	F	55.9	59.3	59.3	59.3
Ovary and Fallopian tube	F	19.2	24.3	36.1	53.2
Uterus	F	?	174.4	157.7	126.9
Breast	F	158.4	170.8	188.4	197.3
Skin other than rodent ulcer, penis, and scrotum	M	?	17.6	17.5	17.1
	F	?	10.9	10.1	10.2
Larynx	M	?	23.9	31.2	28.6
	F	?	6.0	7.1	7.1
Lung and bronchus	M	10.2	12.7	25.1	115.2
	F	7.0	7.0	9.6	26.0
Prostate	M	11.8	26.5	47.3	64.4

Table I. Cancer Mortality. Rates per Million Population (Standardised) at the more important sites for selected years. Data abstracted and rearranged from Table LIX of the Registrar General's Statistical Review for the Years 1938 and 1939, Text. 1947.

INTRODUCTION

That the treatment of cancer is far from satisfactory is generally admitted. The public obviously do not share the enthusiastic claims of some cancer therapists that great "advances" in the treatment of cancer have been made in the last 25 years. In Table I is given an extract from the Statistical Review of England & Wales (Registrar General 1947) summarising cancer mortality trends at various sites since 1901. Also given in Table II are the Comparative Mortality Indices at selected cancer sites for 1951 and 1941 relative to the base year 1938, (Registrar General 1953). (The figures are adjusted for age differences in the populations exposed to risk.) It can be seen that there has been no fall in the incidence of deaths from cancer as an whole. Although at some sites there has been a fall, notably uterus and skin, this is more than compensated by a rise at other sites. Yet at some cancer sites which account for large numbers of deaths, e.g. breast, rectum, the cure rate after treatment is claimed to be about 40%. Assuming that the incidence of cancer at such sites at each age has remained fairly constant then an appreciable fall in the death incidence would have been expected.

The cancer statistics of the Registrar General

TABLE II.

COMPARATIVE MORTALITY INDICES.

Site	Sex	C.M.I. 1941	C.M.I. 1951
Cancer All Malignant Tumours	M	1.01	1.02
	F	0.97	0.93
Buccal Cavity and Pharynx	M	0.87	0.54
	F	0.88	0.89
Digestive Organs and Peritoneum	M	1.00	0.89
	F	0.97	0.84
Respiratory System	M	1.14	2.39
	F	1.05	1.62
Breast	F	0.98	0.96
Uterus	F	0.99	0.77
Other Female Genital Organs	F	0.97	1.10
Male Genital Organs	M	1.07	1.15
Kidney, Bladder, and other Urinary Organs	M	1.08	1.36
	F	1.06	1.28
Skin	M	0.96	0.59
	F	0.86	0.66
Hodgkin's Disease	M	1.03	1.25
	F	0.89	1.10
Leukaemia	M	0.97	1.60
	F	0.96	1.75

Table II. Comparative Mortality Indices (Base Year 1938) at certain cancer sites selected from Table 9 of the Registrar General's Statistical Review of England and Wales for 1951. Adjustment has been made for age differences in the population exposed to risk.

may be inaccurate but they are unlikely to mask an average curability of cancer of about 25% if this were being achieved. Cancer treatment is claimed to be much more effective than it was twenty years ago and facilities for early diagnosis and treatment are much more widespread.

The object of this thesis is to examine the methods of analysis of the treatment of cancer in an attempt to explain the apparent discrepancy between what is claimed for cancer treatment and what is achieved by cancer treatment.

The thesis will be in seven parts:

I. The Difficulties in Evaluating the Value of Cancer Treatment will be examined. These mainly arise from the difficulty in diagnosing cancer and in assessing the degree of malignancy of a known cancer. Unless there is definition of what is being cured the results of treatment are largely indefinite.

II. The Claims for the Curability of Cancer will be discussed and the conclusion will be reached that treatment does not "cure" cancer but at the most prolongs life.

III. The present day Concept of Cancer Behaviour is criticised as are the conclusions relative to

treatment which are based on that concept. An attempt to alter this concept will be made in order to provide an acceptable basis for analysing the behaviour of treated or untreated cancer.

IV. An Index or Formula to Summarise Cancer Behaviour is therefore necessary. The criteria for evolving an accurate index of cancer behaviour will be examined.

V. The Present Methods of Analysing Cancer Behaviour and the Results of Treatment will be criticised and particularly the fallacies of the "five year survival rate" as an index.

VI. An Attempt to Evolve an Accurate and Sensitive Index of Cancer Behaviour will be made. This index it is hoped will overcome as many as possible of the drawbacks of present methods of analysis.

VII. Discussion and Summary.

I. DIFFICULTIES IN THE EVALUATION OF CANCER TREATMENT.

A. Difficulties in Diagnosis.

1. Lack of a Definition.

The word "cancer" has a wide range of meanings. Clinically, it may mean a rapidly fatal disease running its course in a few weeks or a slowly spreading neoplasm which takes 20 years to kill. Histologically, it may mean a basal cell tumour of the skin which may cause no inconvenience if left for 30 years, or a tumour with a certain pattern which the diagnostician thinks might (but will not necessarily), kill the patient in the near future.

This wide range of lesions included in the term cancer is the root cause of all the difficulties in assessing the benefits of treatment of cancer. No one knows whether the results of this form of treatment are better or worse than those of that, because it is rarely that any two treatment clinics deal with groups containing exactly the same proportion of patients comparable with respect to age, degree of malignancy of the cancers, stage of growth, etc.

2. The Fallibility of Histology.

The surgeon, the layman and the lawyer all

have great faith in the part histology plays in the accurate diagnosis of cancer. Although the surgeon may subsequently discover that an histological diagnosis was wrong, he assumes that the histologist was unskilled and that a "better" histologist would have given the correct diagnosis and that absolute truth is achievable. This is not so. The histological diagnosis of cancer is like any other medical diagnosis - the result of weighing up of many and sometimes conflicting probabilities and is itself merely a statement of probability and not an assertion of fact. As in all medical diagnosis the accuracy will vary with the skill of the diagnostician but will never be absolute.

Diagnosis only Prognosis. At the time the diagnosis is made the diagnosis of cancer by histology is only a prediction of its future behaviour. It is a prognosis, and as such is fallible.

A lump found accidentally is called cancer because in the opinion and experience of an histologist it shows characteristics which he has learnt to associate with a subsequently malignant infiltrative behaviour. But other factors beside the histology must be taken into account in assessing the prognosis, such as the age of the patient or the

site from which the tissue has been removed. For example, melanomas of the skin or adenomatous polyps of the rectum occurring in childhood may show the histological patterns which one associates with metastasing malignancy at these sites in the adult. Yet in both cases simple excision is a safe form of treatment and in the great majority metastasis does not and never does occur.

Again, a wedge of tissue removed from the site of a possible carcinoma of the lung, of the skin of the vulva, and of the skin of the hand, may all show an identical histological picture. In the first case the lesion might be diagnosed as cancer with confidence and in the second with doubt. In the third case it might well be given as benign.

Histologically Proven. If a cancer therapist wishes to boast of the accuracy of his diagnoses he usually claims that they are "histologically proven", implying that they possess the absolute accuracy of a mathematical proof. An histologist's opinion is based partly on his own experience but largely on the experience of others reported verbally or in books. Since no two cancers have the identical histological pattern and no two histologists have the same experience nor interpret other men's

experience in the same fashion, "histological malignancy" is an elastic term. There are lesions which all men will call cancer and others which all men will call benign. Between these there is a zone of patterns which some will call one and some the other.

Cancer of the breast is one of the commonest and easiest cancers to diagnose. Yet out of the same hundred cancers diagnosed by one histologist, another histologist will only diagnose 95 and label the remainder as non-malignant, fibrosing mastopathias. In the prostate the debatable zone is even broader, probably up to 15% and in the thyroid might be as high as 50%. Such differences in standards of diagnosis must make comparisons of cure rates invalid.

Overdiagnosis. There is a tendency to overdiagnose cancer and the less skilled the histologist the greater the tendency. It may require skill and courage to refuse to diagnose a lesion as malignant. In case of doubt both the histologist and the surgeon find it easier to call the tumour cancer: the former to avoid the disgrace of "missing" a cancer which later recurs contrary to prediction, the latter because he can now assure the patient (and himself)

that treatment is safe and complete. This tendency is most obvious in cancers at sites such as the breast, lip, skin, prostate, colon or even the rectum where excision of the afflicted area does not lead to gross mutilation.

Overdiagnosis will also occur nowadays because doubtful tissue is examined more often. No lump is now permitted to remain without biopsy whereas fifty years ago many doubtful lumps spontaneously regressed without the benefits of enthusiastic diagnosis and surgery, and were not claimed as cancer cures.

"Early" Cancer. This term is usually used by the histologist as a face-saving formula to get the best of both worlds. If the tumour recurs he diagnosed it correctly; if it does not recur then the surgeon "got it all away". Admittedly there are leukoplakias, "premalignant" mastopathias, "intraepidermal" cancers of the cervix, etc., in which it is difficult if not impossible to predict the probability of subsequent frank malignant infiltration. If these lesions must be called cancer it is better to call them cancers of a low grade of malignancy with low metastasising potential, than to use the word "early" with the meaning that these are

frank cancers at an early stage of their life.

3. The Nature of Present Cancer Treatment.

The ideas of cancer behaviour generally held at present and the rigid separation of all tumours for purposes of treatment into two distinct classes - benign and malignant - strain the impartiality of the histologist or therapist in diagnosis. He must decide immediately whether the lesion is malignant or not malignant; if malignant, treatment must be immediate and radical.

Unless metastases appear later there is no check on the accuracy of the diagnosis and it is only natural that once the diagnosis of cancer has been given and acted upon the record is not easily changed.

B. Difficulty in Assessing Degree of Malignancy.

Even assuming that it is possible to predict with some degree of accuracy that a particular tumour will have metastasising power, it is not possible at present to predict truly the rate of appearance and the number, or even the site, of any metastases which might occur if the cancer is treated or not treated. An estimate of prognosis in the individual case is highly speculative.

The very variability of cancer behaviour has forced those who wish to compare the effect of different treatments to subdivide their cancers into what they believe to be groups of cancers of the same degree of malignancy. In these classifications there is confusion between the inherent malignancy of the cancer, i.e. its growth rate, and the time for which the cancer has been growing. "Early" might mean a cancer of slow but long growth and no wide dissemination, or a highly malignant cancer of short duration which is still localised clinically but which will shortly disseminate. At present two common methods of defining malignancy are histological grading and extent of spread at diagnosis.

Histological Grading. This is not of great value in individual prognosis. It is based on features intrinsic to the tumour pattern, the mitotic activity, degree of differentiation, cellular irregularity, etc. It is well recognised that these vary in different parts of the same tumour and between the secondary and the primary. Also there is little correlation between the factors which are supposed to indicate degree of malignancy, e.g. mitotic activity might be intense in a well

differentiated keratinising squamous cell cancer. Or a widely disseminating sarcoma of the uterus may show no cellular pleomorphism, while a soft tissue sarcoma with a wildly irregular cellular picture and intense mitotic activity may never metastasise after repeated local excisions.

These factors are usually assessed after the outcome is known when other factors, such as extent of spread or clinical rate of growth, give a much better clue to prognosis, and knowledge of which tends to bias the histological grade into which the cancer is put.

Extent of Spread Stages. This has so far proved to be the most reliable guide to malignancy, that is, to prognosis and curability. The extent of spread at diagnosis is the result of all the factors which go to make up malignancy. Of these the most important are:- (1) The inherent malignancy of the cancer. (2) The time for which the cancer has been growing. It is probable that the first of these is by far the most important and the extent of spread found at diagnosis is an indication of this factor.

This method has however its disadvantages. The number of stages into which the extent of spread

can be divided is limited. For even a crude estimate the tissue must be available for histological examination and the processing and examination of multiple areas which might be invaded is expensive and time-consuming. All cancers do not spread in the same step-by-step fashion as does the usual carcinoma of the rectum or the breast. Although melanocarcinoma commonly occurs in a limb it does not necessarily involve the lymph nodes of that limb as a selective route of spread.

Even cancers which have reached the same extent of spread at the time of diagnosis do not behave thereafter in a similar fashion. It is not very rare for a surgeon to excise a breast with its primary cancer and a large mass of invaded lymph nodes in the axilla, and for the patient to survive for at least ten years; whereas a patient with a small cancer the size of a pea histologically of identical pattern with no clinical metastasis, given the same treatment, dies six months later riddled with metastases. There is therefore here a wide variability of behaviour even within the extent of spread stages.

C. Difficulties of Evaluating Cure.

1. What is meant by cure?

The treatment of cancer is at present based on the idea that a malignant tumour grows and spreads as a result of successive uncontrolled proliferations of its constituent cells and that it spreads by direct extension or by emboli to distant sites. By continued growth at these sites and the replacement of vital tissues death will ensue.

The object of treatment, it follows, is to kill or to remove all cancer cells while they are still within the limits of accessibility. According to theory all cancers can be rigidly divided into two classes:-

1. Those in whom the cancer cells have been killed or excised. These patients should all be permanently cured.

2. Those patients from whom the cancer has not been completely removed. Continued growth at the metastatic sites should occur and those patients should die as quickly or nearly as quickly as patients who had no treatment at all. The only value of excision of the primary tumour would be to remove the toxaemia of an ulcerated surface or to perform an anastomosis of some hollow organ which

would otherwise be obstructed by the cancer. In cancers at any site the prolongation of life on the average would not be great and at sites such as the breast would be nil.

But treated cancers do not all behave in this fashion. Outlying cells which have not been removed may lie dormant for ten, twenty or even thirty years before the metastatic deposits suddenly appear and death rapidly ensues. It is difficult to accept that the depression of the activity of the malignant cells was an inherent property of the cells themselves.

The writer has seen a metastasis the size of a tangerine orange removed from the left lobe of the liver at the same operation in which the primary cancer of the lower colon was removed. The patient is alive eleven years later. It is difficult to believe that only one embolus of cancer cells was thrown off to produce a single liver metastasis. Many others must have occurred; yet none of them "took" or has taken. Factors in the host must have played a part in keeping the patient free from further overt metastases.

Such behaviour which is by no means uncommon is difficult to fit into the commonly held ideas of

cancer behaviour. The assumption that treatment plays no part in slowing the rate of growth of the cancer tissue which remains after inadequate removal must be false.

Treatment can reasonably be considered to have one or other of at least three possible effects.

1. It can cure a proportion of cancers and the remainder will progress as if they had never been treated.

2. It can cure some cancers and those patients not cured may have their lives prolonged.

3. There is no such effect as cure, merely prolongation of the survival time. This prolongation of survival will vary and in some cases the freedom from recurrence will persist till death occurs from other causes.

This last seems to be the most probable effect of treatment and this contention will be developed later.

2. <u>The Behaviour of Untreated Cancer</u>.

An appreciable proportion of patients diagnosed as having cancer live for five years after treatment. The claim for at least the partial curability of cancer depends on this undoubted fact. It is of interest and importance to examine if possible the

TABLE III.

NATURAL DURATION OF UNTREATED CANCER.

Site	Number of Cases	Mean Duration in months	Standard Deviation in months	Surviving for five years
Breast	651	38.3	43.33	16%
Uterus	1749	20.9	17.13	3%
Rectum	887	26.7	25.41	5%
Tongue and Mouth	369	16.5	13.21	2%
Oesophagus	299	12.0	10.76	<2%
Larynx	129	14.5	11.25	<2%
Stomach	154	16.8	12.58	<3%

Table III. The Natural Duration of Untreated Cancer from the Time of Onset of Symptoms to Death.
Data abstracted from Greenwood 1926.

behaviour of untreated cancer. If we fix an arbitrary period such as five years as the time after which survivors are claimed to be cured, then even if a few untreated cases survive for this period it will be correspondingly difficult to assess the number of true cures.

Greenwood (1926) collected and summarised the findings of several British authors who had investigated the period of survival from onset of symptoms to death, of patients who suffered from cancer but who received no curative or palliative treatment. These figures are summarised in Table III. It is to be noticed:-

1. Those cancer sites at which radiotherapists or surgeons claim to be able to ensure an high proportion of cures are the same sites as those in which the mean period of survival without treatment is appreciable. (It is noteworthy that these are also the sites at which the surgeon and radiotherapist are prone to indulge in controversy about the relative merits of their respective techniques.)

2. In all six cases the mean survival time is roughly equal to the standard deviation. This measure of the variability of the values is such that roughly 2/3 of the values will lie within the limits

(mean - S.D.) to (mean + S.D.) and about one-sixth of them will have values greater than (mean + S.D.).

We can therefore postulate that for untreated cancer, (and it will be shown that the same is true for treated cancer) the survival times are so variable that roughly one-sixth of the cases will have survival times greater than twice the mean survival time.

(In the tables quoted, time is measured in simple time units and the distributions are undoubtedly skew. If time is transformed to logarithmic units the distributions are more symmetrical. Assuming that the space of time between the point of diagnosis and the earliest deaths is short, then we would expect to find that the S.D. of the distribution in log.time units is approximately one-third of the mean time in log. units. This relationship is in fact found.)

3. It is noteworthy that all the patients of this series died of cancer. There were no doubtful "early" cases. Why they were not treated is not stated in the report, but by far the most likely cause in the majority was that the growths were too widespread or inaccessible for radical treatment at the time of diagnosis,or that the patients were

FIGURE I.

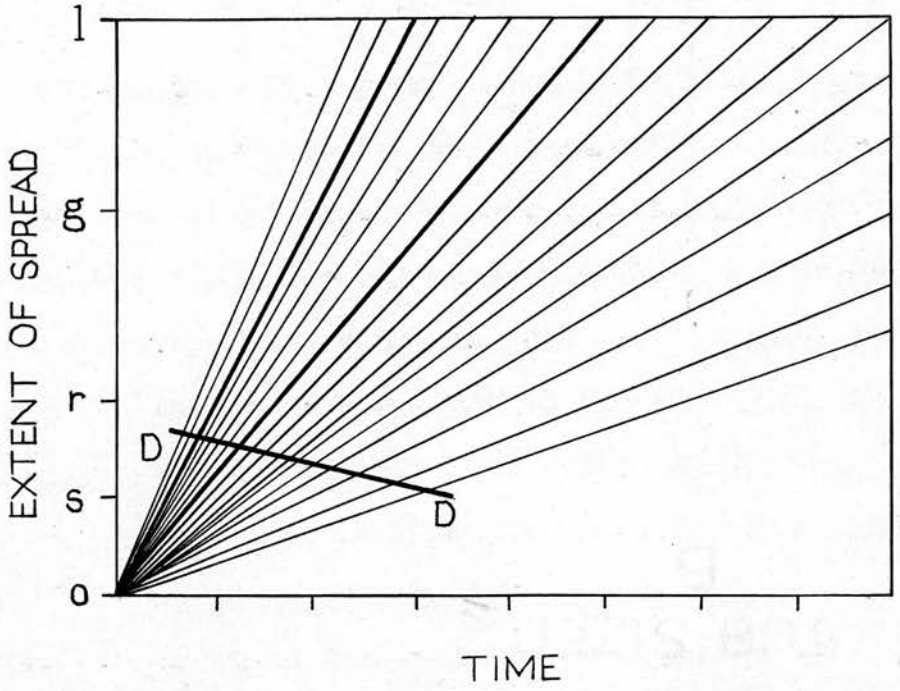

Figure 1. Life Histories of the Individuals of a Series of Cancers.

To show that a small difference in rate of growth at the time of diagnosis results in marked difference in survival time.

The line D - D runs through the points which represent the threshold for diagnosing malignancy in each cancer.

o = Point of occurrence of irreversible malignancy.

s = Appearance of primary cancer.

r = Appearance of first regional metastasis.

g = Appearance of first generalised metastasis.

l = Extent of spread sufficient to cause death.

thought not to be fit to undergo the rigours of treatment. The mean time of survival of all breast cancers (from diagnosis to death) given the full benefits of modern therapy is certainly less than five years. Yet the mean time of survival of what must be considered as the most extensive group of cancers which received no treatment at all was over three years (from first symptom to death).

3. Great Variability of Growth Rate.

In Figure 1 is illustrated in graphical form, the progress from onset of malignancy to death of the individuals in a series of cancers. The abscissa measures time and the ordinate measures the extent of spread. It will be seen that although at the time of diagnosis differences in the rate of spread between adjacent groups of cancers may be so small that with our crude methods of measurement we are unable to detect them, nevertheless a small difference in the rate of growth (diminution in the slope of the line) will be accompanied by a very appreciable increase in the period of survival.

A group of patients with localised and slowly growing cancers considered treatable at diagnosis, would survive longer than the average and give a

mean period of survival much greater than 5 years even in the absence of treatment. If these patients were in fact treated then this increase in survival over the untreated would be attributed to treatment, even although the treatment had no effect whatever. By selection of patients with malignant growths slightly less malignant than the average, or by subdividing the total number of cancers into groups by their degree of malignancy, and only treating the less malignant cancers it is possible to provide almost any cure rate that the therapist desires in the particular group he chooses to treat.

4. Chronicity of Cancer.

Cancer is not only a very variable disease but also a very chronic one. The effect of this is that a therapeutic trial as conducted at present must extend over a long period. Often the man who makes the diagnosis or initiates the treatment is not himself alive to analyse the end results if he has to wait till the majority of the patients have died. What he chose to call cancer at the end of his experiment is often somewhat different from what he called cancer at the beginning. Since the number of cancers seen annually at any one site by one man is relatively small it takes many years, often a

lifetime, to collect a series worth presenting. Most large-scale investigations are derived from collected hospital records extending over a period of fifteen to twenty years. The accuracy and assessment of the individual cases must vary considerably depending on the particular clinician who diagnosed them. The final figures therefore reflect this variability which is not, and often cannot be defined.

Five years is usually considered to be a reasonable period of follow-up for all cancer deaths. While this may be true of cancers such as lung or stomach it is certainly not true of cancers at such sites as breast or rectum. Hence the criticism voiced by some therapists that eight or ten years, or even longer follow-up periods are essential. However, the longer the follow-up period the greater the proportion of patients who are lost sight of, the larger the number who die of intercurrent disease. However much mathematical ingenuity may be introduced in allowing for these defects, there is little doubt that if a treatment does not show better results at any cancer site by the end of five years it is not likely to show them at any time thereafter. If it does, the most likely explanation does not lie in the

efficiency of treatment but in a bias to including a number of cases which were not malignant at all.

5. The Failure to Employ Efficient Methods of Analysis.

In cancer treatment the present day methods of analysing the end results, the figures of which are often biassed and inaccurate, are themselves open to criticism on the grounds that these methods do not take into account these variabilities and allow for them. Mathematical analysis of the results of cancer treatment is rarely performed by a professional mathematician and the results are rarely collected in a way to be of value for adequate analysis.

The Fallacies of Proportions. Nearly all the present methods of presenting cancer statistics use in some way a proportion as does the most commonly used method - the five year cure or survival rate. The difficulty in diagnosis means that the denominator of the proportion is suspect and the difficulty in assessing cure makes the numerator also a doubtful measure. Not only is such a proportion biassed from the start but a proportion is not a very fine statistic. Even if the proportion were derived from unbiassed random sampling the variability in the final figures merely as the result of such random sampling is itself high. For example, the standard

error of a proportion of 45% patients claimed as cured out of 200 cancers is 3.41%. That is, if a further 200 similar cases were submitted to identical treatment then there is one chance in three that the proportion of cures would lie outside the limits 41.6% to 48.8% and one chance in twenty that it would lie outside the limits 38.2% to 51.8%. Using this number of patients, in order to show that this second treatment was significantly superior to the first the five year survival rate in the second 200 cases would have to be at least 52%. By using proportions, if the improvement in treatment is only of moderate degree, hundreds of cases must be used to show this improvement.

The Fallacies of Staging. In cancer at certain sites the curability rate after treatment differs with the "stage" or extent of spread of the cancer at diagnosis. Two series of cancer patients cannot be compared as to curability if they contain different proportions of patients at each stage. To attempt to overcome this difficulty it has now become customary to classify each series into groups by extent of spread stage (or some other attribute gauging malignancy).

However accurately the definition of each stage

is expressed in words, no two clinicians ever interpret the definition or assess the cancers in the same fashion. This subjective error has important consequences when the survival rates of the various stages are compared in the two series.

If the first observer of the same series has a lower threshold for diagnosing and assessing malignancy than the second, then at each stage he will include a number of patients whose cancers were of a lower degree of malignancy than those of the corresponding stage group in the other series. The curability in <u>each</u> stage will be found to be higher in the first assessment because the constituent cancers at each stage are on the average less malignant than in the second. Since the assessment of malignancy at diagnosis is so crude then comparison of stage cure rates in two independently assessed series is not of much value. Staging, unless the assessment is made by the same man in the two series merely perpetuates in as great a degree the error which it was designed to avoid.

As long as present methods of assessing malignancy are so unreliable the only good way of comparing the results from two centres of treatment is to compare the behaviour after diagnosis, whether the

individuals are treated or untreated, killed or cured, of every individual coming for diagnosis to one centre, with every individual coming for diagnosis to the other centre. Preferably the two centres should each drain a fixed geographical area. The random variability of occurrence of different types of cancers in contiguous geographical areas is likely to be much less than the biassed variability that occurs in selection of patients for treatment and inclusion in the five year survival rate.

Summary. The diagnosis of cancer is vague and uncertain. The variability of behaviour of individual cancers at any one site is great even in the absence of any treatment. The methods of counting the cures are crude. We are never sure of what we are claiming to cure and we do not know how much the treatment modifies the behaviour of what we think will prove to be a malignant tumour.

When two series of cases are presented with different cure rates, this difference in the rates is the sum of the differences of at least these factors:

1. The difference actually due to the treatment itself.

2. The differences that might occur merely by

chance in any proportional index particularly if the sample is small.

3. Biassed selection of the cases so that the two series do not contain the same proportion of cancers in each grade of malignancy.

4. Differences in the standard of diagnosis.

There is little doubt the last two factors account for the major part of any differences observed.

II. THE PROOF OF THE CURABILITY OF CANCER.

Some modern cancer therapists have ceased to talk of cure as their objective and are satisfied with a prolongation of life, presumably because cure is difficult to achieve or difficult to measure. If cancer is as curable as is claimed and our current ideas of cancer behaviour are correct then the effects of treatment should be made obvious

1. In a fall in the death rate.
2. In the fact that the earlier the diagnosis the higher the cure rate.

1. That the expected fall in the death rate has not occurred is obvious from examination of Tables I & II. If the death rate from cancer had fallen it would have been claimed as proof of the efficiency of treatment. Since it has not, then its absence is most likely due to the ineffectiveness of treatment. No valid argument has been brought forward to suggest any other conclusion.

2. Since the object of treatment, certainly surgical treatment, is to eradicate the primary site of growth before it has spread beyond the limits of surgery, then the earlier the treatment is undertaken the less extensive the cancer and the higher

the hope of cure.

Yet when the figures correlating cure rate and the duration of symptoms are examined the expected correlation is not found. Walters Gray & Priestley (1941) found on examination of the records of 11,000 cases of cancer of the stomach that 2,840 were considered suitable for resection of at least part of the stomach. Of the patients with resectable cancer, 45% had a duration of symptoms of less than one year before treatment, while in the others not suitable for resection 54% reported a duration of less than one year. When the relationship between survival and duration of symptoms was examined it was found that those patients whose symptoms were present for less than one year the five year survival was only 25% whereas for patients whose symptoms had lasted more than one year the five year survival rate was 32%.

Similarly Lane-Claypon (1926) found that 58% of breast cancers of stage II with a five year survival rate of 25% had symptoms of less than 6 months, while the proportion of cancers in stage I with a survival rate of 75% who had symptoms of less than 6 months was 63% - a proportion not significantly different from the stage I cancers.

Park and Lees (1951) investigated this problem

in more detail with respect to cancer of the breast and came to the conclusion that published figures failed to confirm the assumption that earliness of diagnosis was correlated with curability.

The usual and probably correct explanation for this "paradox" is that the more rapidly growing cancers have a shorter duration of symptoms before treatment and a shorter period of survival after it. But this does not explain the absence of the supposed relationship between duration of symptoms and curability. With the large series of cases which have been examined such a relationship ought to be detectable if it exists. Although the variability in malignancy of cancers which have shown symptoms for 6 months may be very wide, according to theory the overall cure rate (or average survival time) for an identical group of cancers treated at 4 months ought to be much greater. The difference should represent that proportion of the group which spread from the curable into the incurable zone in the two months.

Again, according to Dukes (1940) the surface area of a primary cancer of the rectum at the time of treatment is roughly constant. (The size of the primary cancer in any particular part of the rectum

required to produce equally intense symptoms would not be expected to vary by very much.) But Dukes also states that there is no relationship between the size of the primary and the extension of the secondary deposits at diagnosis. From this one might make the inference that the occurrence of metastasis bears no relationship to the duration of the symptoms. Since curability is proportional to extent of spread one can reasonably argue that duration of symptoms before treatment bears no correlation with curability.

Extent of spread at diagnosis at any site is not an indication of the time for which the cancer has been growing but rather an indication of its inherent malignancy or rate of spread. The principal correlation with long survival after diagnosis is not the earliness in diagnosis but the inherent low malignancy of the cancer.

Conclusion. From this we conclude that treatment of cancer does not prevent metastases if these are going to occur and in those cases which it is effective at all it merely prolongs life. How effective it is, is difficult to determine from the data usually presented in cancer statistics.

III. THE THEORIES OF CANCER BEHAVIOUR AND THEIR INFLUENCE ON TREATMENT.

The Present Concept of Cancer and Its Influence on Treatment.

The dissemination of a cancer has been considered to occur an appreciable time after the appearance of the primary, leaving an interval sufficiently long to permit diagnosis and successful eradication of the primary in many cases.

The opinion has been expressed in the last paragraph that treatment based on this hypothesis has not proved very effective. This does not of course prove the theory wrong since obviously cancer does start locally, but it does suggest that in many, if not the majority of cancers dissemination occurs before the diagnosis of the primary cancer is possible.

Treatment directed to complete eradication of the primary cancer often, perhaps always, fails to prevent metastases if these are going to occur, while treatment of the accessible tumours often has surprisingly beneficial results, even when it is known that all involved tissue has not been removed. Removal of a tuberculous kidney or lobe of a lung often does restore a patient to relative good health although no surgeon would claim he had excised all

the tubercle bacilli in the body. Whether the patient recovers or not depends largely on restoration of his immunity by the removal of an infective mass and diminishing for a time the virulence of the infection. It is possible, that in a patient suffering from cancer, removal of a malignant mass may restore the "immunity" or growth control equilibrium to the body so that metastatic deposits are temporarily suppressed. Such a theory would explain the occurrence of secondaries twenty five years after removal of a primary cancer or the regression, admittedly usually temporary, of the secondary deposits after the primary is removed.

Surgery. Since cancer has been assumed to be a local disease its treatment could be claimed to lie in the province of the surgeon. In spite of great advances in surgical and anaesthetic technique permitting longer operations and wider fields of excision, the results of surgery are not impressive in the treatment of the great killing cancers such as lung, stomach, breast and colon. Yet surgery, if the cancer is accessible, is the most logical and probably the most efficient form of treatment since it does at least remove the malignant cells in the field of operation.

Radiotherapy. The object of radiotherapy is to kill all the malignant cells by subjecting the area of infiltration to a penetrating beam of X-Rays. Unfortunately, the lethal effect of irradiation on the cancer cell is not specific and the cancer cell is more susceptible than the normal cell only in so far as it is more rapidly dividing and metabolising. The limiting dose in the use of radiotherapy is therefore the lethal dose for normal tissue. While it is possible that radiotherapy might sterilise a superficial area from malignant cells, at deeper levels it is almost certainly inferior to surgical excision of the affected area if this is localised. It has the advantage over surgery, however, that it can reach areas inaccessible to surgery. However the "magna therapia sterilans" which the radiotherapists claim must be rarely, if ever achieved.

The full usefulness of surgery and radiotherapy have been already exploited to the full and little more can be expected from those techniques.

Chemotherapy. So far no drug has been introduced which will cure cancer, nor in fact any drug with the possible exception of stilboestrol, which will appreciably slow the growth rate of a malignant tumour. Hundreds of drugs have been

tested which will inhibit temporarily the growth of cancers in mice and some of them have been tried in the human, but without success. Any injurious procedure applied to a mammalian body, including the human, which bears a cancer will temporarily reduce the growth rate of the cancer. This is again merely the result of the increased susceptibility of rapidly proliferating tissue to injury by non-specific toxic or traumatic procedures. These chemotherapeutic agents are effective (temporarily) in direct proportion to their toxicity - that is they have a low therapeutic ratio (Lees & Lees 1951). It is doubtful if any chemotherapeutic agent known at present equals radiotherapy in efficiency.

A Concept of Cancer.

Since the current concept of cancer behaviour is unacceptable because it fails to explain the observed facts, it is necessary to attempt to evolve a theory which will be compatible with the facts.

If possible an attempt should be made to reconcile the vast amount of information collected in the last 20 years about induced animal cancer with what is known about human cancer. (As far as the radiotherapist and surgeon are concerned they would carry out exactly the same techniques as they

use at present if no experimental research had been done at all.)

In most definitions of cancer by pathologists the adjective "uncontrolled" or "uncoordinated" is usually applied to the growth of the tumours conveying the impression that some higher mechanism does, in fact, exert a controlling influence on the organisation and function of each normal tissue. That any tissue is under the influence if not the control of numerous other tissues is self-evident. But it is only recently that attempts have been made to investigate experimentally the influence of general natural "controlling" factors in the host on the growth rate of induced tumours, and little investigation in the human has been made so far. Most pathological writers although they may have defined cancer in some way as an "uncontrollable" growth nevertheless systematically classify cancers according to common sites. An investigation and subdivision of cancers by their mode of behaviour has therefore been rarely attempted and modern pathologists e.g. Willis (1948), still cling to a "local" classification as opposed to a "general" or "behaviourist" classification of cancer.

Much difficulty could be avoided if cancer were

considered to be a local manifestation of a systemic disease. Cancers arise through a failure to control growth on the part of the body as a whole, - cancer is a degenerative systemic disease which frequently results in death. More attention might be paid to the factors which result in the failure of control rather than the results of the failure, i.e. the discernible tumours themselves. It has a resemblance to hypertensive arteriolar disease in which one tissue may fail to function adequately and lead to death of the whole. But just as in cancer, the tissue which ultimately fails may be any one of many.

At birth each tissue can be postulated to be endowed with a functional life span. During the life span of the tissue the intensity and amount of activity which it undergoes is dependent partly on internal metabolic factors brought to bear on it by other tissues, and partly by external factors present in the environment in which the body moves. The external factors may influence the specific tissue directly, or indirectly.

A tissue can then be assumed to be hereditarily endowed with a certain number of metabolic cycles. When these are expended death will occur and the

TABLE IV.

AGE INCIDENCE OF CANCER.

FEMALES.

Age Group	Cervix	Breast	Respiratory System	Stomach	Large Intestine	Haemopoietic System	Buccal Cavity & Pharynx	Total
30 -	27	48	17	16	16	46	4	255
35 -	52	155	37	44	37	47	6	525
40 -	93	288	54	64	65	59	12	889
45 -	139	448	96	123	114	63	26	1454
50 -	220	564	141	201	189	93	30	2219
55 -	282	732	213	304	294	127	48	3114
60 -	313	831	293	607	455	163	58	4174
65 -	322	994	396	994	714	189	83	5699
70 -	303	1145	424	1499	1150	209	115	7489
75 -	430	1448	469	2193	1812	234	150	9637
80 -	316	1735	487	2793	2524	178	185	12400
85 +	394	2402	409	2667	3091	136	318	14203

Table IV. Mortality Rates per Million Living by Age and Sex for Some Common Cancer Sites.

Derived from Tables 1 and 17 of the Registrar General's Statistical Review of England and Wales for 1951.

TABLE IV. (Contd.)

AGE INCIDENCE OF CANCER.

MALES.

Age Group	Prostate	Bladder, etc.	Respiratory System	Stomach	Large Intestine	Haemopoietic System	Buccal Cavity & Pharynx	Total
30 -	1	3	34	21	15	55	3	236
35 -	1	5	119	50	32	66	4	446
40 -	4	22	243	129	55	80	13	774
45 -	8	54	607	255	90	105	20	1501
50 -	34	153	1220	470	162	137	41	2841
55 -	93	151	1837	782	276	179	98	4515
60 -	256	279	2365	1283	458	222	161	6668
65 -	646	419	2765	1808	862	325	307	9494
70 -	1216	552	2470	2520	1494	322	543	12475
75 -	2091	732	2038	3062	2172	255	1005	16051
80 -	2524	859	1665	3071	2665	265	1000	17353
85 +	3149	1084	1153	2787	2632	189	1187	18204

Table IV. Mortality Rates per Million Living by Age and Sex for Some Common Cancer Sites.

Derived from Tables 1 and 17 of the Registrar General's Statistical Review of England and Wales for 1951.

tissue will cease to integrate with the other tissues. This tissue death may take the form of atrophy and fibrous replacement or it may take the form of independent proliferation, i.e. neoplasia.

By this hypothesis, as far as the human is concerned, the most important cause of neoplastic development is merely tissue exhaustion from the normal wear and tear of survival. In only a few cases e.g. tar cancer, osteomyelitis sinus cancer, some bladder cancers, is a tissue subjected to a known abnormal external stimulus which will precipitate exhaustion to the onset of malignancy. The mammalian body starts to die of cancer from the moment of conception. The principal "cause" of human cancer is ageing. This is very clearly brought out in Table IV culled from the Registrar General's figures for 1951. From this it will be seen that at the common cancer sites the incidence increases steadily with advancing age.

Chemical carcinogenesis in the experimental animal or the human can be considered to arise because the tissue is subjected to an abnormal stimulus as the result of the presence of the carcinogen. The allotted span of metabolic cycles would then be used up more rapidly. The action of

these compounds in the causation of cancer can be compared to the action of the sulphonamide drugs in inhibiting the growth of bacteria.

When a carcinogenic hydrocarbon is applied to a tissue, then some of it is absorbed within the cell and because of its resemblance to a natural steroid is taken into the metabolic cycle. Since it is not identical with the normal steroid the particular enzyme system into which it has been incorporated fails to complete its chain-reaction cycle and either stops short or continues in an abnormal fashion. If the amount of the carcinogen within the cell is high then death of the cell results. If it is low, because of its insolubility and because it is firmly fixed chemically to some cell constituent, then the cell will survive with an impaired enzyme system. To compensate for the failure of part of the enzyme system the remaining enzyme systems must work over-time or, possibly the disorganised enzyme system is subjected to further strain. If the cell is subjected long enough to these abnormal conditions then a "mutation" will occur. By successive cell division a race of cells will develop which will be capable of survival without the use of a particular group of enzymes which are essential for survival of

the normal cell. Function of these new enzymes is no longer dependent on integrated control and a race of malignant cells arises which are capable of a semi-independent existence.

Such an hypothesis will explain the continuous graduation of malignancy, i.e. degree of infiltrative and metastasising capacity which is found in human cancer. Degree of malignancy will roughly parallel the number and the importance of the enzyme systems which the malignant cell has developed independent of the control of the host. There is no necessity to postulate a sudden irreversible change in the cell before which it is normal or benign in character and after the change it is irretrievably malignant. Although a sudden irreversible alteration in one enzyme system may occur, before the onset of frank clinical malignancy such alteration may have to occur in a succession of enzymes. The number and type of abnormal independent enzyme systems required to induce this state will vary from tissue to tissue and from individual to individual and from time to time. The steps on the road to malignancy are made of enzyme systems or potentials for differentiation and not of cells. Minor degrees of abnormality will not necessarily lead to malignant neoplasia, either

because the host regains control over the proliferative activity of the group of abnormal cells or because of failure of the new abnormal enzyme systems to survive.

Influence of the Concept on Choice of Method of Analysis.

By this conception cancer can be considered as the resultant between the attempt at autonomous growth on the part of the tissue and the attempt of the body to re-exert its ordered control over that growth. If the local growth asserts its autonomy then it need not necessarily grow and spread at a constant rate.

Once however the cancer starts to infiltrate, even although its apparent rate of spread is slow, emboli are being thrown off. If the host still has an high degree of control none of these emboli will take. When however the primary cancer achieves a certain volume, the partial control of the malignant cell diminishes even further and a metastasis may take. There is not only to be considered the growth rate of the primary mass of cancer cells which is probably logarithmic, but also the metastasising potential which will depend partly on the size of the primary mass itself. The reaction

between the host and the cancer can be compared to the law of mass action in chemistry. The rate of spread will depend on the "concentration" of malignant potential in the cancer cells and the "concentration" of anti-cancer factors in the host. By removing a large mass of primary growth the rate of the reaction might be slowed or even halted and the equilibrium restored. When more is known of the science of cancer and we are able to measure more accurately the factors involved it might be possible to devise some formula to predict rate of spread similar to that which the chemist uses to predict the rate and direction of a chemical reaction.

At present however all we can do is to measure what factors we can and find out how long it takes the patient to die. By examining the behaviour of a series of cancers we might by working backwards be able to derive some general law.

This contention that for practical purposes cancer should be considered as incurable has been misunderstood,(that is cancer which it is believed possesses metastasising power). Firstly, it has been interpreted to mean that all present treatment is useless. This is not so. No such assertion

was made. What is meant is that, although treatment may be of little avail on the average, the odd case occurs in which it is highly effective. But nobody so far has investigated why it was effective in the odd case.

Secondly, it is held that when the surgeon excised an "intra-epidermal" carcinoma of the cervix he can legitimately claim to have cured a cancer if the patient lives to the natural period and does not die of cancer of the cervix. It is impossible to deny that these cases have been prevented from the possibility of dying of cancer of the cervix but it is equally impossible to deny that many of the "premalignant" lesions would never have become infiltrating cancers. It is necessary to deal in terms of the average survival of a group of patients with similar "premalignant" lesions. Assume there is a one in five chance that a premalignant lesion of the cervix will become malignant five years later and will kill the patient three years after that. The survival period of this patient is eight years compared with the twenty five years of the other four. This gives the survival of untreated premalignant lesions of the cervix as just over 23 years. By amputating the cervix in all five women the surgeon

can claim to have increased the survival of patients with such lesions from 23 to 25 years.

To refuse to call these successful treatments "cures" may be quibbling. But every normal tissue is potentially malignant and if it is argued that after removal of premalignant tissue it is justifiable to claim a cancer cure then the extreme form of this argument is that every woman should have the breasts and uterus excised at the age of 35 since these are two sites at which the probability of malignant change is high. The surgeon would cure the great majority of cancers of the breast and cancers of the uterus but might find these patients still developed cancer at some other site later.

Even if the claim that excision of a premalignant lesion prevents a cancer death is accepted, such treatment will have a negligible effect on the overall cancer death rate. There is no harm in regarding the object of treatment as the diminution in the number of cancer deaths and not as the increase in the number of cures. This objective is often forgotten in the competitive presentation of cure rates.

Summary.

1. The principal "cause" of cancer in the human is ageing. With our present knowledge a search for specific "causes" is likely to prove barren in the foreseeable future and hence the chance of "preventing" cancer is not very great.

2. The behaviour of the host, i.e. the behaviour of all tissues other than the malignant tissues, is of equal importance to that of the cancer in determining the period of survival after overt tumour or tumours have appeared.

Any method of assessing curability of cancer should, if possible, indicate the relative importance of any factor in the host, the cancer or the treatment which has played a part in causing or preventing the patients' death. Cancer research in the human has been dominated by the cellular morphology of the tumours. Other and possibly more important factors in the cancer and the host have been largely ignored.

3. The adoption of this attitude to the cancer patient would not alter present methods of treatment by very much but by considering the patient as well as the cancer facts might come to light which would give us understanding of the cancer process and prove of value in treatment and prognosis.

4. In view of the multiplicity of possible "causes" most of them unknown, treatment at present can only be and is, of a non-specific type. A single chemotherapeutic substance which will specifically inhibit the growth of most or all cancers (and have little or no effect on non-neoplastic tissue) is unlikely to be found. Antibiotics are effective against a wide variety of organisms which possess a common (normal) enzyme system which can be inhibited. But the same abnormal "malignant" enzyme system may never occur in two cancers since no two cancers are ever identical in behaviour.

5. Since Radiotherapy and Surgery in cancer treatment are unlikely to advance further and since the science of the chemotherapy of cancer is in its infancy, the prospects of rapid advances in cancer therapy in the foreseeable future are small. The drug that sets us on the road to success will be one which merely prolongs life. Our methods of analysis must be sensitive enough to appreciate even a small average prolongation of life. The benefits of treatment show a continuous gradation and cannot be assessed in all or none terms.

IV. AN INDEX OF CANCER BEHAVIOUR.

The Best Index of the Effects of Treatment.

It is required to obtain a numerical index which will summarise cancer behaviour with or without treatment. The index should fulfil these criteria:-

1. It should be simple.
2. It should be applicable to and suitable for all cancer types whether treated or untreated.
3. It should be applicable to present and future forms of treatment.
4. It should indicate, if any, the beneficial effects of treatment. These should be shown as early as possible after the start of the experiment.
5. The accuracy of the index of the behaviour of the group of cancers under discussion should be so defined that the significance of any difference from that of another group can be estimated by methods which will satisfy the statistician.
6. The data from which the index is derived must show the relative importance of any factor in the cancer itself or in the host or in the treatment, which might have played a part in the final outcome. Only thus can advances be made.
7. The index and data should be presentable in such a way that their validity is unquestioned. If

possible, the examination of the figures themselves should give an indication of the accuracy of the clinical assessment on which the claim for the treatment is based.

The Benefits of Treatment. We wish then to estimate the benefits to be derived from cancer treatment insofar as these can be given a numerical value.

The ideal benefit is complete cure. At many cancer sites complete cure cannot be assumed even if the patient survives for twenty or more years. Conversely treatment might alleviate pain and misery and not necessarily increase the number of cures although it might be still highly beneficial.

But it is unlikely that any treatment which "cured" some cases of cancer, assuming that such a form of treatment exists, would not also prolong the life of those who were uncured. Although it might have little influence on the misery of the terminal stages it would prolong the period of relative well being preceding them. The object of treatment then, is to prolong life.

In assessing the benefits of cancer treatment, although there are other factors which are immeasurable and yet important, the easiest factors to measure accurately are those involving time and of

FIGURE 2.

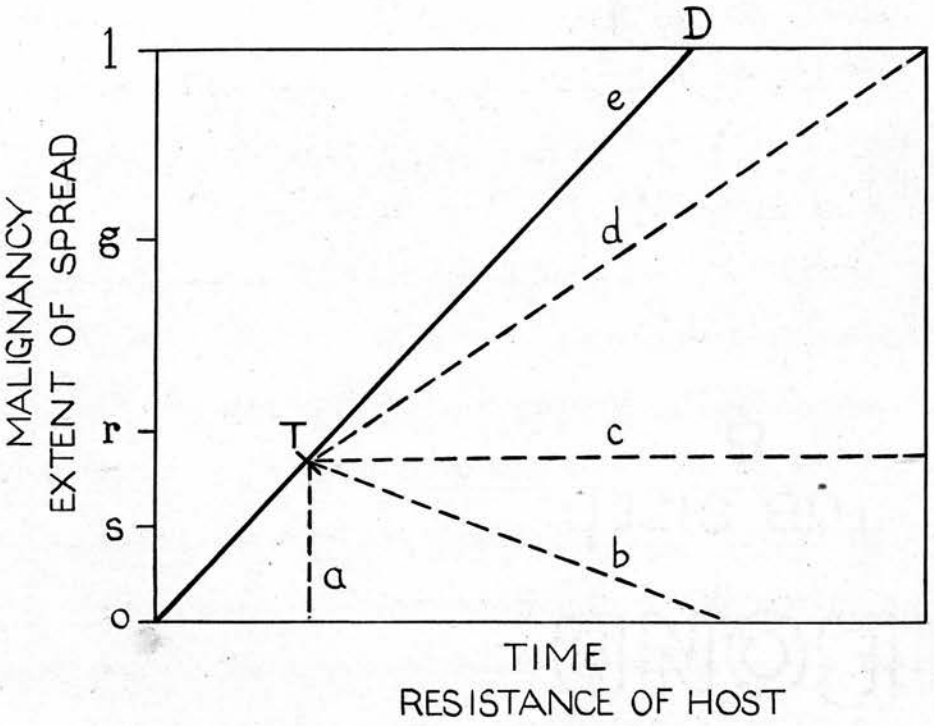

Figure 2. The Life History of an Untreated Cancer and the Possible Effects of Treatment.

T = Point at which treatment given.
D = Point of death.
a = Immediate cure.
b = Regression to disappearance.
c = Arrest of growth.
d = Progression at a slower rate.
e = Treatment ineffective.
o,s,r,g,l, as in Figure 1.

these the time from diagnosis to death is the simplest and the most reliable.

The best treatment will be that which prolongs the life of the greatest proportion of patients. The best index will be that which summarises simply and accurately a formula applied to estimate this prolongation of life.

What Do We Wish to Measure? Basically we wish to evolve an index or formula which will measure the growth rate of a cancer with or without treatment.

The problem can be put graphically. In Figure 2 the ordinate measures the proliferativeness of the cancer, that is the extent of spread at any point in the life of the cancer. The abscissa measures the resistance of the host, that is the time the cancer takes to achieve a certain degree of extension or to cause death. The life and rate of spread of an untreated cancer are represented by the line OD, O being the point of origin of the cancer when irreversible malignancy set in, and D the point of death. The ordinate can be measured in stages of the life of the cancer such as clinical appearance of the primary tumour, occurrence of local metastases, generalised dissemination.

If we could fix two points on this line before

treatment we could calculate its slope (i.e. the growth rate of the cancer), and by producing the line from the point of diagnosis and treatment (T) find the point at which the cancer tissue would be of sufficient bulk to cause death. (The assumption is made that the growth rate is constant during the life of the cancer. This may not always be correct.) If the patient were treated and the growth rate thereafter observed, having fixed the point T we could plot the subsequent course of the cancer after treatment.

The possible courses of the cancer are shown by the dotted lines in Figure 2 namely (a) immediate cure, (b) regression to disappearance, (c) arrest, (d) progression at a slower rate, or (e) progression at the same rate. The change in the slope of the line after treatment or the difference between the time of death after treatment and the expected time of death without treatment will be the measure of the value of treatment.

Unfortunately -

1. We have no accurate method of assessing the rate of growth after treatment and still less before it.

2. The point T on the line cannot be fixed

FIGURE 3A.

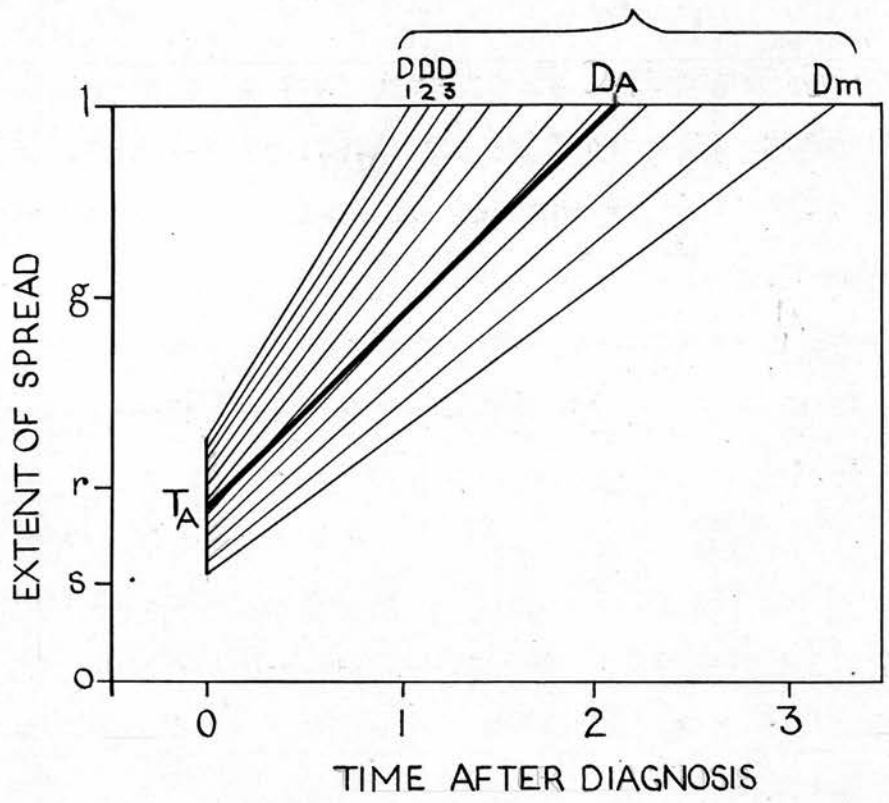

Figure 3A. The Behaviour after Treatment of the Individuals of a Series of Cancers thought to be of the Same Degree of Malignancy at the Time of Diagnosis.

T_A = Average of extent of spread in the individuals at the time of diagnosis.

$D_1, D_2 - - D_m$ = Times of survival of individual patients after diagnosis.

D_A = Average time of survival after diagnosis.

o,s,r,g,l, as in Figure 1.

with any certainty since we do not know accurately the extent of spread or the point in its life history which the cancer has reached at the time of diagnosis.

3. We accordingly do not know exactly how the cancer would have behaved in the absence of treatment.

The only coordinates we know with certainty are those for death and the point of time at diagnosis (as measured backward from the death point). The coordinate for extent of spread at diagnosis is ill-defined.

The behaviour after treatment of a group of cancers all of which as far as could be judged clinically were of the same degree of malignancy and all of which had passed through the same fraction of their life history at the time of treatment is illustrated in Figure 3A. We can only assume that the average figure for the group for the extent of spread coordinate of T lies somewhere near the centre of the zone within which the coordinates of extent of spread at diagnosis of all the cancers are presumed to lie. By measuring the time interval from T_A to D in every member of the group we get the average time of survival D_A after treatment and can calculate the

FIGURE 3B.

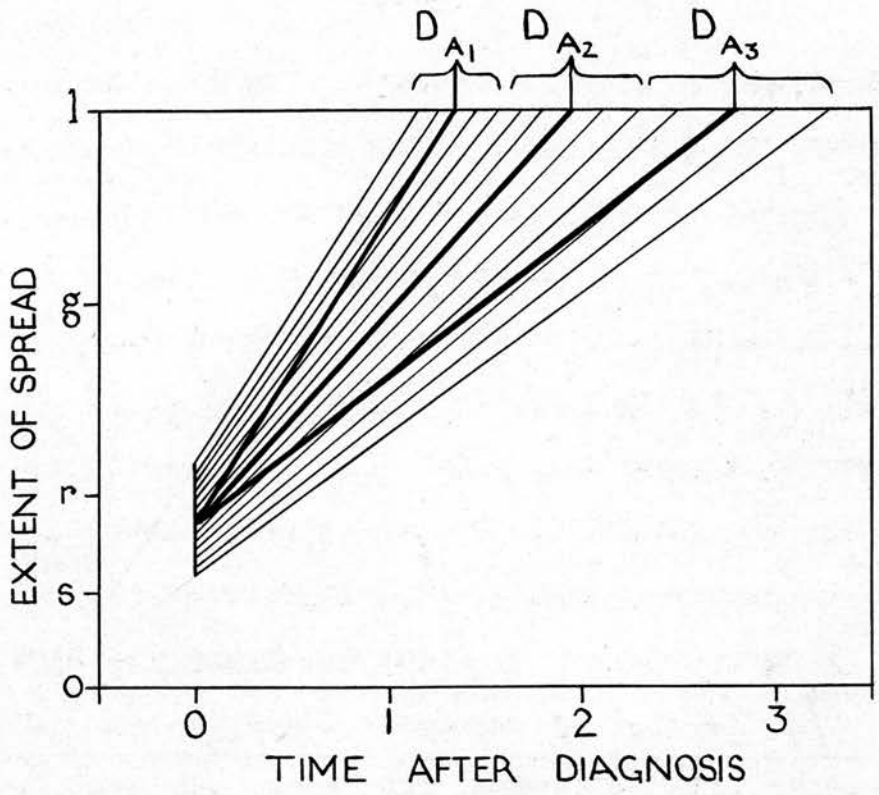

Figure 3B. The Subdivision of the Series of Cancers shown in Figure 3A into Three Groups by Means of a Factor Known to Influence Malignancy and possessing Three Degrees of Intensity.

D_{A1}, D_{A2}, D_{A3} = Average time of survival of the individuals in each of the three groups.

variability round this average. We thus measure crudely the average rate of growth after treatment.

By the measurement of factors which we believe would influence or be associated with the growth, we might be able to more accurately define the rate of growth and so diminish the variability of behaviour as measured round the point D_A. Our group of cancers might be subdivided by classification by a further factor of which three degrees of intensity can be recognised. Provided the intensity of this factor is related to the rate of growth the main group could be subdivided into three subgroups whose behaviour could be diagrammatically shown in Figure 3B. The variability of behaviour is thus seen to diminish within each subgroup and we are able to more accurately define the points D_{A1}, D_{A2}, etc., and the slopes of the lines after treatment. For the disentanglement of the relationship of each factor to one another and the influence of each factor on the growth rate it will be necessary to resort to mathematical analysis of the data by "analysis of the variance" or by "analysis of multiple regression lines". Graphical representation has however much value in showing possible trends and relationships and does not demand an high degree of mathematical

skill as these procedures do.

Ideally these measures of the average rate of growth after treatment should be contrasted with what would have been the average behaviour without treatment of the same group of cancers. Possibly by examination in retrospect of the data of the results of treatment we might get some idea of the behaviour without treatment. Since at present we cannot even compare the treated cancers with another exactly similar group of untreated cancers then it is only possible to use some indirect standard for comparison. This in effect means comparison with the behaviour of control patients who did not have cancer, or preferably with that of an exactly similar group of cancer patients treated by another method.

Comparing the Efficiency of Established or New Treatments.

It is frequently argued that it is unjustifiable to carry out trials of new methods of treatment on patients because we might deprive the patient of established and reasonably good treatment for the doubtful benefits of a new treatment. There is however no other way of assessing the value of a new treatment. If common sense and medical judgment consider it hopeful, then it is justifiable to carry

out a trial provided it is carried out in a fashion which will give a definite result - better, worse or equally good. To obtain this result the best planned experiment will be that which uses the minimum number of patients and the minimum time.

The following points are of importance in planning such an experiment.

1. If the new treatment is a drug then its possible mode of action and its dosage should be investigated in the laboratory before it is tried in the human. Some attempt should be made to predict its toxicity and therapeutic ratio - how specifically is the drug antagonistic to cancer cells and not just to cells in general?

Merely because a drug, chosen for no particular reason, has been shown to inhibit transplanted tumours in mice is no justification for therapeutic trial.

2. The type of cancer first chosen for test should be one with a narrow range of behaviour or one in which the cancers can be divided into groups of uniform malignancy. Although any general chemotherapeutic agent which was effective against one type of cancer would be unlikely to have no effect on another, the choice of say bronchogenic carcinoma

which is almost invariably and rapidly fatal means that if the drug had any inhibitory effect at all it would be quickly obvious with even a few cases.

The Leukaemia-Lymphosarcoma-Hodgkin group of cancers are most frequently used for drug trials but they are not satisfactory. The range of behaviour in the group is very wide and more important, it is very difficult to forecast the subsequent behaviour of any member of this group of cancers with our present methods of diagnosis. To show a significant effect therefore there would be required a very large number of patients unless the effect was very striking. Since the cells of this group like their normal counterparts are highly susceptible to non-specific toxins, there is a tendency to claim "encouraging results" after treatment by what was merely non-specific toxaemia.

3. The treatment should theoretically be given as early as possible in the course of the disease since it is probable that in this way it will be most effective in prolonging life. The immediate beneficial effect might be most obviously found in a moderately advanced cancer of moderate malignancy where the change in growth rate would be more easily observed.

Usually however untested treatment is likely to be first tried out on patients with cancers in which other treatment has failed or which are untreatable by other means. It is mainly for this reason that the unsatisfactory haemopoietic group of cancers are commonly used for trial of a new drug.

4. Apart from those involving time the choice of the factors by which we can measure the value of treatment is difficult. The advance of the tumour as indicated by the number, extent, and site of the metastases would be the best guide since cancer by and large kills by its mechanical bulk. Unfortunately this is difficult to assess clinically and in some cancer types like leukaemia, chemotherapy may produce massive necrosis of malignant cells without necessarily prolonging life; (such treatment may even shorten it).

Similarly, in assessment of the patient's health, the change in body weight or other general measure often fails to show correlation with the progress or regression of the cancer.

5. The results must be interpreted with common sense. The validity of the conclusions drawn from the results will depend largely on the accuracy of the assumptions which were put forward

at the start of the experiment. By altering the assumption it is possible to draw two entirely different and sometimes diametrically opposite conclusions from the same results.

For example, Stocks (1952) found that the incidence of cancer of the lung in urban districts in England & Wales is roughly proportional to the density of the population. One cannot quarrel with this mathematical correlation.

Now Stocks started with the assumption that an important factor in the causation of lung cancer was the inhalation of carcinogenic substances present in the atmosphere as the result of industrial pollution.

Since atmospheric pollution increases with industrialisation and concentration of population, his findings led him to assert that his assumption was correct and that industrial smoke was an etiological factor.

But an entirely different assumption could be made, (which is the more probable one in the writer's opinion). The facilities for the diagnosis and treatment of surgical chest conditions are concentrated in specialised units. These units tend to be located in densely populated areas although the patients sent for treatment might come from suburban

or rural areas. Deaths are registered in the district in which the patient died and not in the district of domicile. The assumption is made that the incidence of lung cancer deaths in any town is proportional to the number of beds available for diagnosis and treatment of that disease in the town.

The findings confirm this assumption and imply that industrial smoke is not an etiological factor in cancer of the lung.

6. The principal source of error and confusion in cancer statistics lies not in the mathematical analysis of the figures themselves. It is the method of collection of the data which is suspect. However elaborate the subsequent analysis, this will never compensate for biassed judgment by the therapist at the time of diagnosis and treatment.

7. If possible, the results should be presented in such a fashion as to permit them to be contrasted with the behaviour of untreated cancer.

The Conduct of the Therapeutic Trial. Briefly the experiment will be carried out in this fashion.

1. The type of case to be used for trial should be defined.

2. Every case of this type coming to the clinic must be included in the experiment.

3. Any factor in the host or the cancer which might influence the effect of treatment or a change in which might indicate the efficiency of treatment should be measured. This measurement should if possible be made by someone who will not carry out either the control or the test treatment.

Some variable factors such as duration of symptoms can be given numerical estimation, others might be only recordable as being present or not present, while others can only be roughly divided into three or four degrees, as in recording state of health. These measures however crude will have statistical validity provided they are made by an unbiassed judge.

4. The patient is then allocated purely by chance to one or other treatment, e.g. by the toss of a coin, or by allocating alternatively to each treatment.

5. The patient is then treated.

6. After an appropriate interval the patient is again reviewed preferably by the original assessor and preferably by one who does not know which treatment each patient has had. The factors previously assessed but which might have altered as the result of the advance of the disease or of the effect of

treatment are again measured. Those patients who die under treatment should if possible be similarly assessed at the time of death and certainly the time of death recorded.

7. The figures are analysed by a professional statistician who will assess with stated degree of accuracy the probability that any differences in behaviour between the two groups was due to treatment. He will also assess the importance of any other factor which might have influenced the end result.

It is customary at this point to add that, of course the statistician should have been called in in the first place before the experiment began. This cannot be denied. Unfortunately the mathematician cannot make the clinical measurements to ensure these are unbiassed. Nor can he usually suggest which factors are likely to be important in the outcome. These can only be determined by the clinician whose clinical skill and judgment of cancer will be decisive in the choice of factors which he considers important.

While accuracy in assessment is important since it will diminish the variability in the individual survival times in each class, what is much more

important is that the standards of diagnosis should be the same in the two series being compared. Overdiagnosis of cancer by 5% is relatively unimportant provided that the non-cancer patients are as likely to be subjected to one form of treatment as the other. If the radiotherapist insists on himself making the selection and stratification of patients which he considers suitable for radiotherapy and the surgeon permits the surgical pathologist to do the stratification for him, then the two series are not comparable since the standards of assessment are not the same. Unless like is being compared with like, tests of significance are misleading.

It is also necessary to emphasise that the initial assessment (however crude) of the characters of the tumour must be made at the time of diagnosis. Assessment in retrospect with knowledge of the outcome, will be subject to so much self deception, that the figures will be worthless.

V. CRITICISM OF PRESENT METHODS OF ANALYSIS.

Before an attempt is made to evolve a method of analysis which will permit the measurement of the benefits of treatment in the fashion suggested the two common methods of recording cancer results will be discussed.

The Five Year Survival Rate.

The five year survival rate fulfils only one of the criteria of a good index, namely simplicity. Apart from this it has many disadvantages. These spring mainly from the fallacies - that cancer diagnosis is certain and is either positive or negative, that treatment is entirely curative or completely ineffective, and that cancer at any site behaves in an uniform manner. The principal disadvantages can be listed.

1. The five year survival rate is not a true index of the value of treatment. It implies that in the absence of treatment the survival rate at five years would have been nil. At some cancer sites the survival rate at five years for untreated or even untreatable cancer is appreciable. A five year survival rate after treatment should be contrasted with the survival of similar cancers without

treatment. We are interested in the increase of survival time due to treatment and at present our idea of the survival of treatable but untreated cancer is very vague.

2. By only recording the number alive at five years it fails to indicate the benefits to those who died within five years, but whose life was prolonged appreciably but not quite for five years. Nor does it indicate the benefit to those who would have lived for five years without treatment.

3. It assumes that death from cancer if it is going to occur occurs within five years. Since even at those sites which are claimed to be partially curable, the rate of dying after the fifth year of cancer patients is still greater than the rest of the population, this assumption is clearly false.

4. Although 5 years is the longest period for which patients can be followed with any degree of accuracy or convenience there is no reason why five years should have been chosen as the ideal time at which to show the maximum value of treatment at all cancer sites. Treatment might increase the survival time of all bronchogenic carcinomas by 100% yet the five year survival might still be less than one per cent. Assuming that some cases of

bronchogenic cancer can be cured by treatment then this would be obvious by three years, when about 98% of treated and untreated cancers at this site would have been dead.

5. The survival rate is a proportion and cannot be any more accurate than the numerator or denominator of that proportion. The principal error is likely to lie in the denominator due to selective overdiagnosis of cancer and the survival rate ignores or exaggerates this error.

The numerator is less open to criticism since the number of survivors at five years can be counted although they may not be "cured".

6. As the result of failing to measure other possible benefits of treatment at other times the data can only be divided by one attribute - survival for five years. Such a proportion is subject to great random variability between sample and sample drawn from the same mass of cancer patients at any site.

7. It is difficult to assess the effect of treatment on those patients who die from other causes or who are lost sight of before five years. If patients who die of intercurrent disease are excluded no account is taken of the influence of the cancer in

precipitating death or of treatment in delaying death. The failure to attend may be due to death from cancer.

This source of inaccuracy can be partly corrected by the construction of a Life Table and so obtaining the mortality rates for each year based on the number known to be alive at the beginning of the year. From this the probability of survival to the end of each year up to the fifth can be calculated. This procedure of course only minimises one of the fallacies in the collection of the data themselves and does not correct the errors of the five year survival rate as such.

The Survivor Table and Curve.

The survivor table is a useful method of presenting the results of cancer treatment and it has many advantages over the five year survival rate which only uses the figures for the end of the fifth year. The data can be presented graphically by plotting the number of patients alive at the end of each year (or other period of time) against the units of time. The numbers surviving may be plotted either as absolute numbers or more commonly as percentages of the original total treated, in order to

TABLE V.

SURVIVAL OF PATIENTS WITH CANCER OF RECTUM.

Extent of Spread Stage	Percentage Surviving at End of Year									
	1	2	3	4	5	6	7	8	9	10
A	96	92	87	84	83					
B	93	87	77	70	62					
C_1	91	74	58	46	41					
C_2	61	34	23	15	12					
Total	78	62	51	46	41	37	34	31	28	26
D	44	15	7	4	2					
Control	98	96	94	92	89	86	83	80	77	74

Table V. Percentage Survivors at End of each Year after Diagnosis, of Patients with Cancer of Rectum treated by combined Abdomino-perineal Excision. (Data taken from Graphs of Dukes (1944) and only approximate.)

A, B, C_1, C_2 = Stages of extent of spread of cancer at time of diagnosis and treatment.

D = Cases unsuitable for radical excision and treated by palliative colostomy.

Control = Control population of same age and sex distribution as cancer patients.

FIGURE 4.

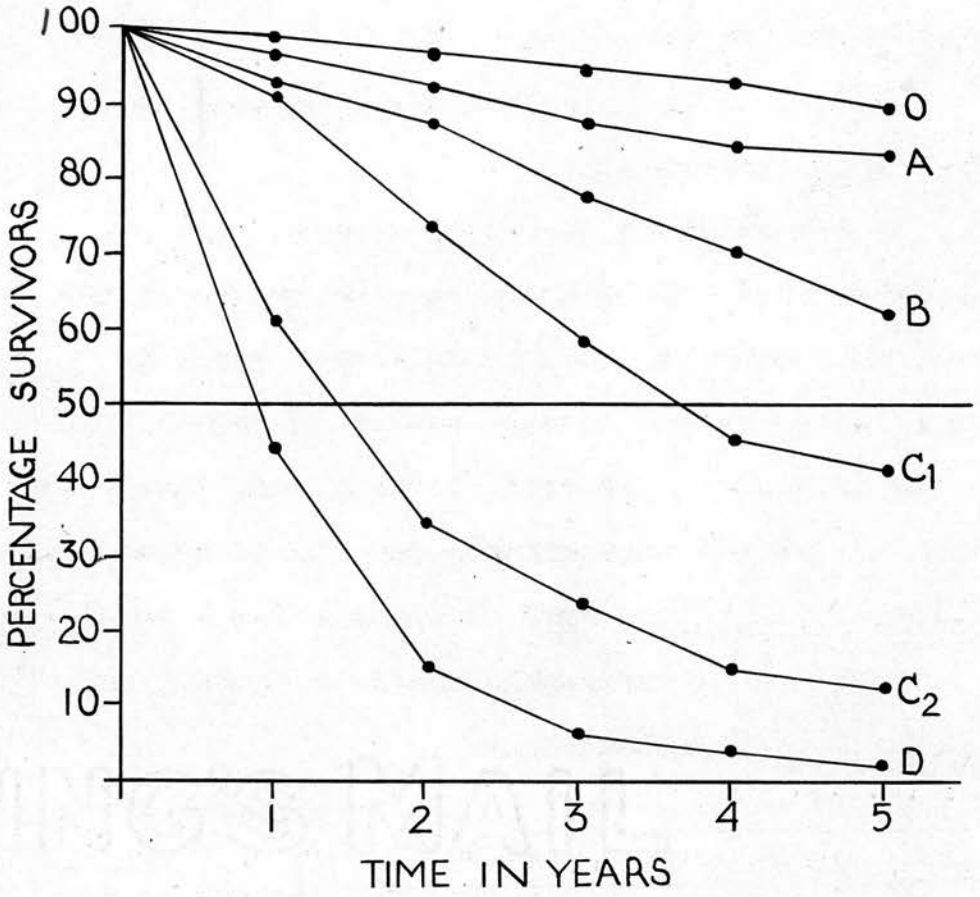

Figure 4. Percentage Survivors of Cancer of Rectum at the End of Each Year after Diagnosis (Duke's data).

A,B,C_1,C_2 = Extent of spread Stage at time of diagnosis.

D = Cases unsuitable for radical surgery and treated by palliative colostomy.

O = Control population of same age and sex distribution.

be able to compare series.

In Table V and Figure 4 are presented the data of Dukes as an example.

If the survivor curves of several series of cancer patients are plotted as percentages on the same scale then the area beneath each curve is proportional to the average number of years lived by the individuals in each series in the follow up period. We can thus quickly see the relative merits of two forms of treatment or compare the treated with a control non-cancer population or a control untreated cancer population.

In Figure 5 are shown five such survivor curves:-

I. Control population of non-cancer patients.

II. All operable cancers of the rectum, Stages A, B, C_1, C_2. (Dukes 1944).

III. All cancers of the rectum coming to hospital. (Dukes 1944).

IV. The curve of 887 patients with cancer of the rectum who for some reason were not treated. (Greenwood 1926). Time is recorded from onset of symptoms in this curve.

V. Inoperable cancers of the rectum, Stage D. (Dukes 1944).

FIGURE 5.

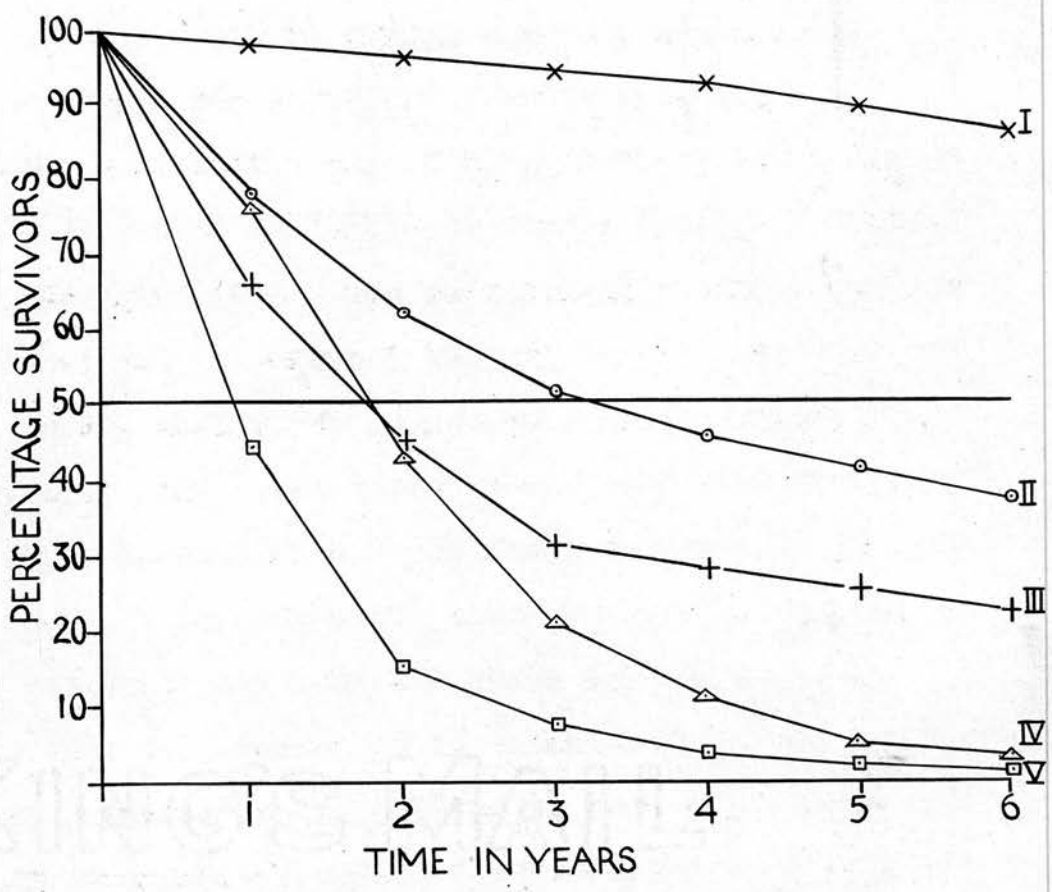

Figure 5. Percentage Survivors of various Classes of Rectal Cancer Patients at the End of Each Year after Diagnosis.

I. = Control population.

II. = All operable rectal cancers, (Dukes 1944).

III. = All rectal cancers coming to hospital, (Dukes 1944).

IV. = Untreated rectal cancers, (Greenwood 1926). Time is measured from onset of symptoms in this class.

V. = Rectal cancers receiving palliative treatment only, (Dukes 1944).

Examination of these curves shows:-

1. The area between the third and fourth curves gives an indication of the number of man-years saved by the most modern treatment of cancer of the rectum. This difference is small when compared with the survival time of untreated cancer. Yet the five year survival rate of cancer of the rectum after treatment is claimed to be about 40%. The inspection of this simple graph gives a much better idea of the scanty effectiveness of treatment.

2. Inspection gives the best time at which to assess the relative value of treatment. A new treatment might show no superiority as measured by the five year survival rate but at two three or four years the proportion of survivors might be appreciably and significantly higher.

3. By presenting the survivors at the end of each year or shorter period of time on a graph we get a form of regression line. In Figure 6 are two such survivor curves. The patients were submitted to two different forms of treatment, A and B. If we could estimate the mean time of survival and the slope of each line we would be able to apply tests of significance between the lines representing the two treatments. The mean time of survival is

TABLE VI.

NUMBER OF DEATHS IN EACH YEAR AFTER TREATMENT.

Treatment	Deaths in each Year after treatment					Survivors at end of fifth year	Total
	I	II	III	IV	V		
		Survivors.					
A	126 74	89 37	65 24	49 16	40 9	40	200
B	228 72	186 42	141 45	105 36	75 30	75	300
Totals	146	79	69	52	39	115	500

$\chi^2 = 17.070$ $n = 5$ $P_{.01} = 15.09$

$P_{.001} = 20.52$

Table VI. Data shown in Figure 6 and arranged in a table for the estimation of χ^2.

FIGURE 6.

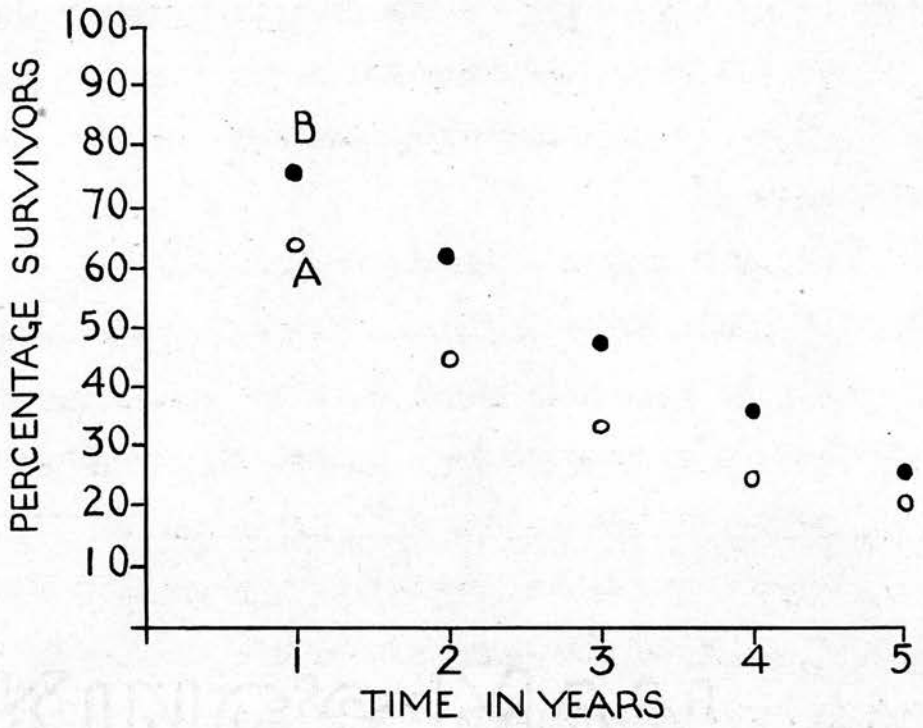

Figure 6. Percentage Survivors at the End of Each Year after Diagnosis in Two Imaginary Series of Cancer Patients, Each Series being subjected to a Different Form of Treatment.
Data as in Table VI.

difficult to estimate because we can only guess the time of survival of those who live more than 5 years, (e.g. by assuming that they lived for five and one half years). This method of analysis is therefore not feasible.

A simple method of making use of all the survival times is to apply a χ^2 test. The deaths occurring in each year along with the survivors for five years are arranged in a table, as in Table VI.

Making the assumption that there was no difference between the treatments the probability of finding such distributions of death by chance in two successive random samples is less than one in an hundred. It can be concluded that treatment B is better than treatment A. If it was thought that there was a tendency to overdiagnose cancer in one or other series and that the survivors included cases which were not cancer at all the analysis could be made by deaths only, and this would minimise the effects of error in diagnosis. Although not of such an high degree of significance the result is still significant.

From the graph it is seen that the treatment is most effective in prolonging life in the first three years and it is of interest to note that the

superiority of treatment B can be shown even at the end of the first year (χ^2 test $P < \cdot 01$) and becomes increasingly significant at each successive year.

This method is superior to the five year survival rate because it makes use of more of the information which is available and so more clearly defines the behaviour of each group after treatment. Its superiority in sensitivity is shown by the failure of the five year survivor index to be significantly different in the two series when analysed by the χ^2 test or the standard error of the difference between two proportions.

Summary.

The five year survival rate as an index of the effect of cancer treatment conceals so many fallacies that little reliance can be placed upon it in comparing the results of different forms of treatment.

The survivor table is better. It is simple, applicable to all cancer types, and may indicate the benefits of treatment, if any, long before five years. It does not, however, indicate the factors which influence prognosis nor does it overcome the difficulty of assessing the malignancy of the cancers which are being treated.

VI. A SUGGESTED INDEX OF CANCER BEHAVIOUR.

1. The Problem.

In attempting to assess the survival or curability of a group of patients we have at least two groups of variables.

Firstly, there is the variability of the factors influencing the malignancy of the individual cancers.

Secondly, there is variability in the factors in the host which influence the reaction to a malignant tumour. Even if we could rigidly define the degree of cancerousness of a malignant tumour all the patients with that particular degree would not die simultaneously.

It is possible in the second case to define accurately the variability in survival. There is no doubt that the individual times from diagnosis to death can be accurately measured if the follow up is long enough and thorough enough. Nevertheless we might not be able to measure the influence of the individual factors or even be aware of their existence.

The real difficulty lies in defining the variability in the assessment of the degree of malignancy at the time of diagnosis.

Much might be gained in the study of cancer if cancer were considered analogous to an infectious disease or toxic lesion in which the advance or regression of the lesion depended on the interplay between the virulence of the infecting organism and the resistance of the host. Since both of these might vary independently if we wished to find a relationship between virulence of the organism and time of dying, we are presented with a problem identical with that in cancer.

Modern biological statistics have been evolved to elucidate such complicated bacteriological and pharmacological problems. It is regrettable that they have never been applied to the problem of cancer.

2. <u>The Median Lethal Time - (M.L.T.)</u>.

Since the five year cure rate is now becoming discredited it is necessary to evolve some simple measure which will summarise cancer behaviour.

For illustration, the extent of spread of cancer of the rectum found at diagnosis will be used as a measure of the inherent malignancy of the tumour, without considering the period of time for which the tumour has been growing. Other attributes of the

FIGURE 7.

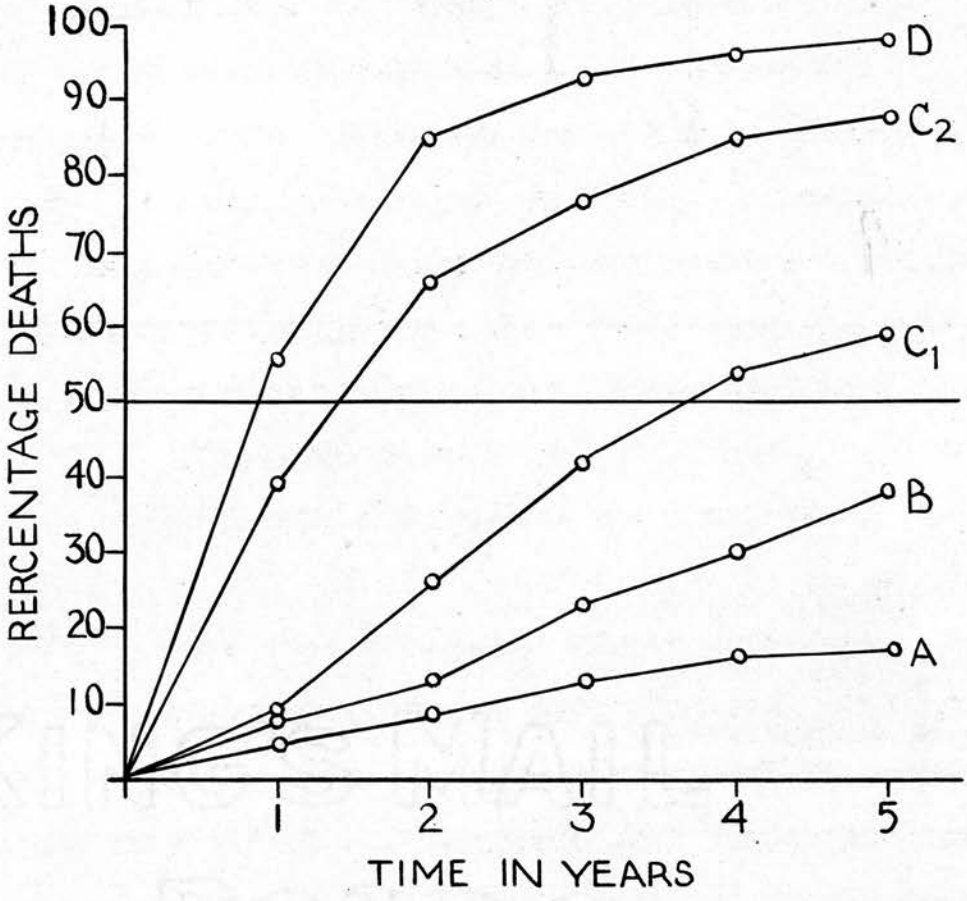

Figure 7. Cumulative Percentage of Deaths of Rectal Cancer Patients at the End of Each Year after Diagnosis.

Simple Time Scale.

A,B,C_1,C_2,D, = as in Figure 4.

host or cancer will be ignored in the meantime.

For reasons to be given later, it is more convenient to plot, not the number of survivors, but the number of deaths in cumulative fashion. In Figure 7 are recorded the cumulative percentage of deaths at the end of each year after diagnosis of patients with rectal cancers which were in Stages A, B, C_1, C_2 and D, at the time of diagnosis. (D = most extensive stage = unsuitable for radical surgery.)

According to the assumption made, these curves show the rates of dying of groups of patients, each member of the group having a cancer of roughly the same degree of "cancerousness". In the less malignant groups the final deaths occur well beyond the limits of feasible follow up. In these the upper limit of survival may be unknown, and it is not possible to calculate accurately the mean period of survival or the standard deviation. Under such circumstances we can summarise our data by another average in place of the mean - namely the median.

In the Figure an horizontal line at the level of the 50% death point has been drawn, and the median lethal time can easily be read off. It is not necessary to draw a graph but a visual representation

is useful in showing any sudden alteration in the rate of dying which might have significance. An improved form of treatment will lead to a "shift to the right" of the death curve with increase in the median lethal time.

The Advantages of the M.L.T. These are:-

1. The first 50% of deaths occur within a relatively short time of diagnosis and accurate long term follow up is of less importance.

2. A patient who dies is more easily counted than a patient who survives for an indefinite period.

3. If the patient dies within one or two years it will be easier to establish whether he did die of cancer, or of an unrelated disease.

4. At cancer sites such as the breast and prostate, overdiagnosis of cancer is the rule. In the death curve, since the slope of the curve is steepest round about the 50% death point, inclusion of a few patients who did not have cancer and who survive for a long period will only result in a relatively small increase in the median lethal time of the group. But their inclusion would considerably increase the five year survival rate or the mean survival time of the group.

5. In the division of a series of cancer

patients into sub-groups, clinical and histological criteria are so vague that borderline cases occur in which opinions may justifiably differ.

The patient who is placed in a group of a higher grade of malignancy than is correct will, on the whole, die later than the other members of the group into which he is placed. When the cumulative death curve is plotted, the majority of those patients incorrectly included will die among the latter 50% of the cases and will not affect the 50% death point to any extent. The reasoning is the same as under para. 4.

5. If a more effective method of treatment were applied one would expect it to be most obvious, not in those who would live a short time nor a long time, but in the intermediate lengths of survival. Even a small increase in the true average survival time would shift the curve significantly to the right.

We are, in fact, measuring principally the rate of dying of the more rapidly dying half of any group.

By using the median lethal time as an index of survival or curability, the grosser errors of the five year survival rate are avoided. This index, in fact, takes much less trouble to compile than the

five year survival rate. It is easily comprehended.

Need for a Measure of Variability. The principal disadvantage of a proportional index is that a proportion shows such wide variability in random sampling from the same population. If we replace this by an average, namely the median, we must define the expected variability to be found in this average when different samples are drawn from the same population.

As a measure of the dispersion round the median value, we could calculate the quartile deviation Q, where $Q = \frac{Q3-Q1}{2}$ and Q3 and Q1 are the upper and lower quartiles of the sample. But this value cannot be extended to further statistical treatment and a similar objection is made by statisticians to the standard error of the median.

It is therefore necessary for the definition of variability round the average value to translate the median value into some other statistic which would be more suitable for the calculation of its error and more intricate analysis.

3. Suggested Method of Analysis.

In any experiment designed to estimate drug toxicity, it is found that individual animals show considerable variation in the time of exposure to a

fixed dose of the drug before death occurs. If groups of animals are given increasing doses of the drug then it is found, as one would expect, that the higher the dose the sooner, on the average, the animals in that group die.

With any particular dose, when the cumulative death - time curve is plotted it is found to be of sigmoid shape, which becomes more symmetrical if time is plotted on a logarithmic scale. When the frequency distribution is plotted against logarithmic time scale it has been found that this latter curve is approximately of the "normal" symmetrical type, and for practical purposes is assumed to be so. That is, the frequencies of individual times of dying are found to be normally distributed provided time is recorded on a logarithmic scale. It follows from this that the median lethal log. time and the mean lethal log. time are the same.

It is always much easier to grasp the importance of a relationship between two factors if their relationship can be expressed as a straight line on a graph. Assuming that a frequency distribution curve is normal, the abscissa can be measured in units of the standard deviation (S.D.) of the distribution - plus or minus from the mean value - that is, in

FIGURE 9.

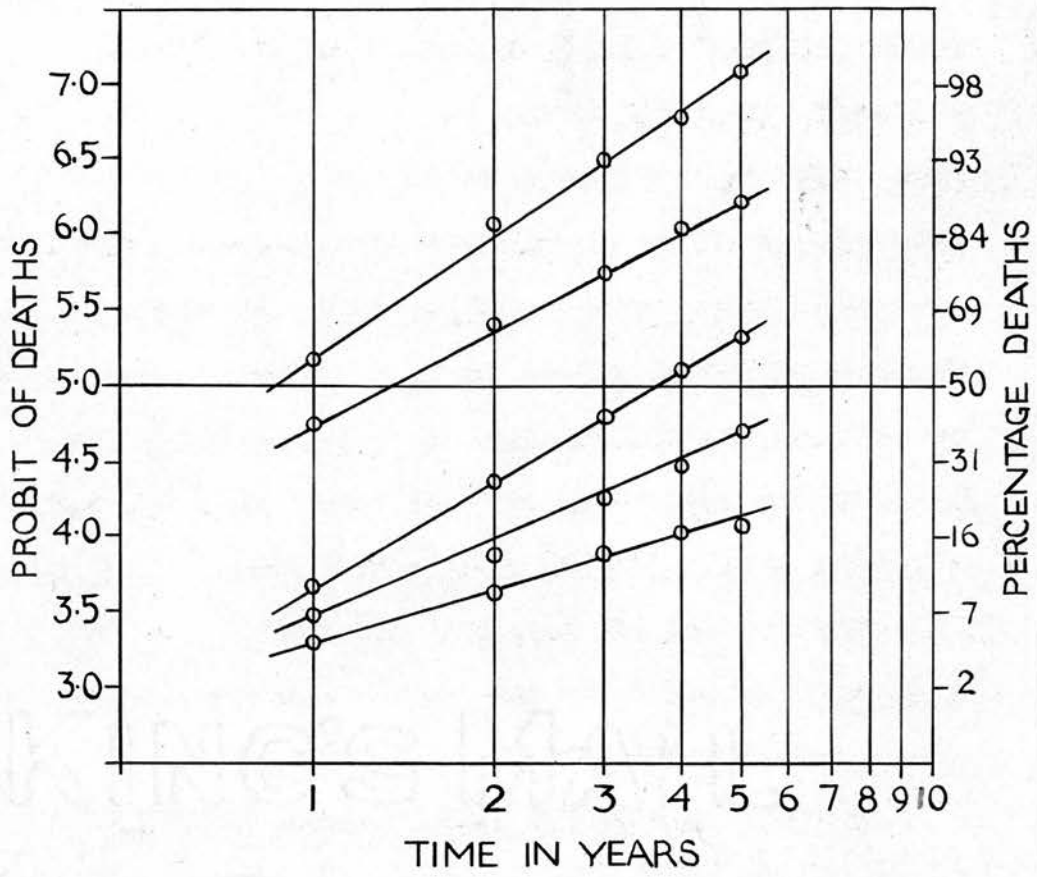

Figure 9. Probit Transformations of Percentage Deaths of Rectal Cancer Patients.

Logarithmic Time Scale.

Data as in Figure 4.

FIGURE 8.

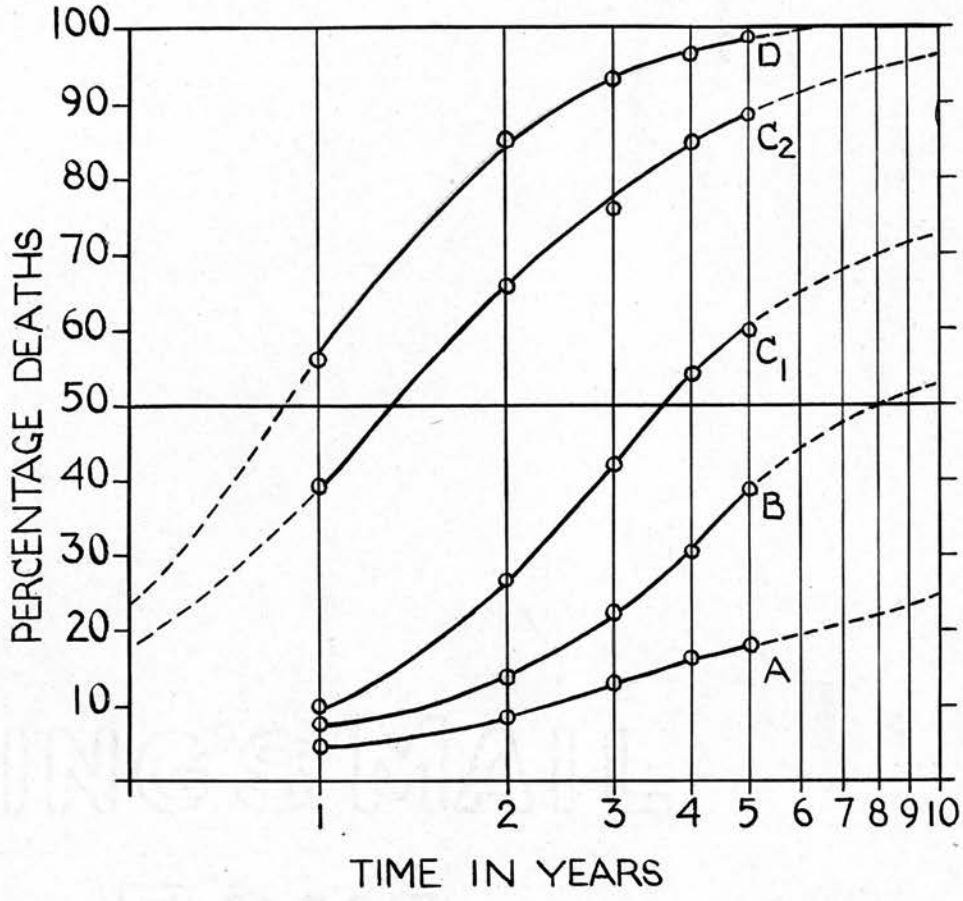

Figure 8. Cumulative Percentage of Deaths of Rectal Cancer Patients at the End of Each Year after Diagnosis.

Logarithmic Time Scale.

Data as in Figure 4.

"standard measure". An ordinate raised at a point corresponding to any particular value of S.D. measured along the abscissa plus or minus from the mean, will cut off an area to the left of the ordinate which is a constant percentage of the total area under the curve, provided it is of "normal" type. If we plot the standard deviate corresponding to the proportion which have died by a particular time, against the logarithm of that time, then the points obtained should lie on a straight line. (In order to avoid the use of negative deviates it is now customary to add 5 to the normal deviate and obtain the "probit" value.)

In this particular case, dosage is the controlled variable.

The time-cumulative mortality curves of our subgroups of rectal cancer patients are, in fact, sigmoid curves. The curves are again more symmetrical if the time is measured on a logarithmic scale - Figure 8. The probit transformation of these distributions results in relatively straight lines - Figure 9. The hypothesis can be put forward that - <u>The Frequencies of the Logarithms of the Times of Survival after Diagnosis of Individual Patients bearing Cancers of the Same Degree of Malignancy are Normally Distributed</u>.

The hypothesis is applied empirically as a convenient method of analysing the data but there is no reason why the data should necessarily conform to it. It may be that some other method of relating time to number of deaths might give a more symmetrical "normal" distribution.

The groups of human animals behave as if they had been injected with different doses of that drug called "cancerousness" which has a long continued slow-acting but nevertheless frequently ultimately lethal effect.

Fitting the Regression Line. The Estimation of the Mean and Standard Deviation. Calculation of Standard Error of Mean.

If all or nearly all the patients of the Stage died, the procedure for fitting the regression line would be as follows:-

1. The individual times of dying would be recorded and ranked in order of time of death.

2. Since in cancer statistics the numbers are usually large, it will be necessary to "group" the individuals into 10 to 20 subdivisions for easiness of handling. (If the number is less than 30 or so the individual times of dying would be conveniently used.) The class interval (time) should be chosen

on the logarithmic scale for ease of computation later, that is, the original times up to which deaths are recorded should be in geometric progression - 1 week, 2 weeks, - 4, - 8, - 16, - 32 weeks etc.

3. The cumulative distribution up to the end of each interval is then calculated and converted to a percentage of the total distribution.

4. The standard deviates or probits corresponding to these percentages are obtained from statistical tables (e.g. Fisher & Yates Table IX) and these probits are plotted against the upper limits of the corresponding class intervals.

5. The best fitting line through these points can be drawn by inspection. Any systematic deviation of a group of points from the line representing the major portion of the distribution can be seen. Such systematic deviation is most likely to occur at either or both ends of the distribution. (This will be discussed later.)

6. If the distribution is normal that is, if most of the points lie close to the line, then an estimate of the mean (log.) time of dying can be made by finding the point at which the regression line cuts the ordinate for 5 probits (= 50% deaths). An estimate of the standard deviation (S.D.) of the

distribution can also be found and this will be that period of time (in log. units) measured along the abscissa which corresponds to 1 probit (= 1 S.D.). The slope of the line will then be $\frac{1}{S.D.}$ where the ordinate is measured in probits and S.D. is measured in log. units. In cancer data with its large numbers, this graphical estimate of the mean log. time and standard deviation (in log. units) will be reasonably accurate for the calculation of the standard error of the mean and for application of tests of significance.

The mean and standard deviation can be converted back into the simple time scale e.g. in weeks.

7. The graphical estimates of the mean log. time and its standard deviation can be checked by calculating from the original data (Bliss 1937).

As far as can be ascertained Boag (1948) was the first to suggest the use of the log. time-mortality distribution in cancer statistics. This work has been unfortunately ignored probably because the method of application suggested by him was too complicated for clinical use. It is felt that his attempt to predict the percentage of "cures" at a fixed time after diagnosis, and to use this as an index, introduces unnecessary difficulties.

Regression Lines: (Incomplete distributions). Only rarely will the times of dying of all the patients in each stage be available for calculation and even if they were, they may not be considered suitable for inclusion in the calculations.

1. Apart from the more malignant stages of most tumour types, the period of feasible follow up is not long enough to include all possible deaths.

2. The plotted points commonly lie on a fairly straight line until the upper end of the distribution, where they "tail off" and deaths occur less frequently than expected, - see Figures 9 & 14. The explanation is as follows.

In animal experiments every animal in the group receives the same dose. But in human material all the patients in each stage do not have cancers of exactly the same degree of malignancy. We are, in fact, recording the distribution of times of dying of patients who might bear a tumour of one of a range of degrees of malignancy. Each degree of malignancy would have its own distribution of deaths. The frequency distributions (normal) of times of dying of groups of patients with three closely related degrees of malignancy can be represented in Figure 10A and the probit transformations in Figure 10C.

FIGURE 10.

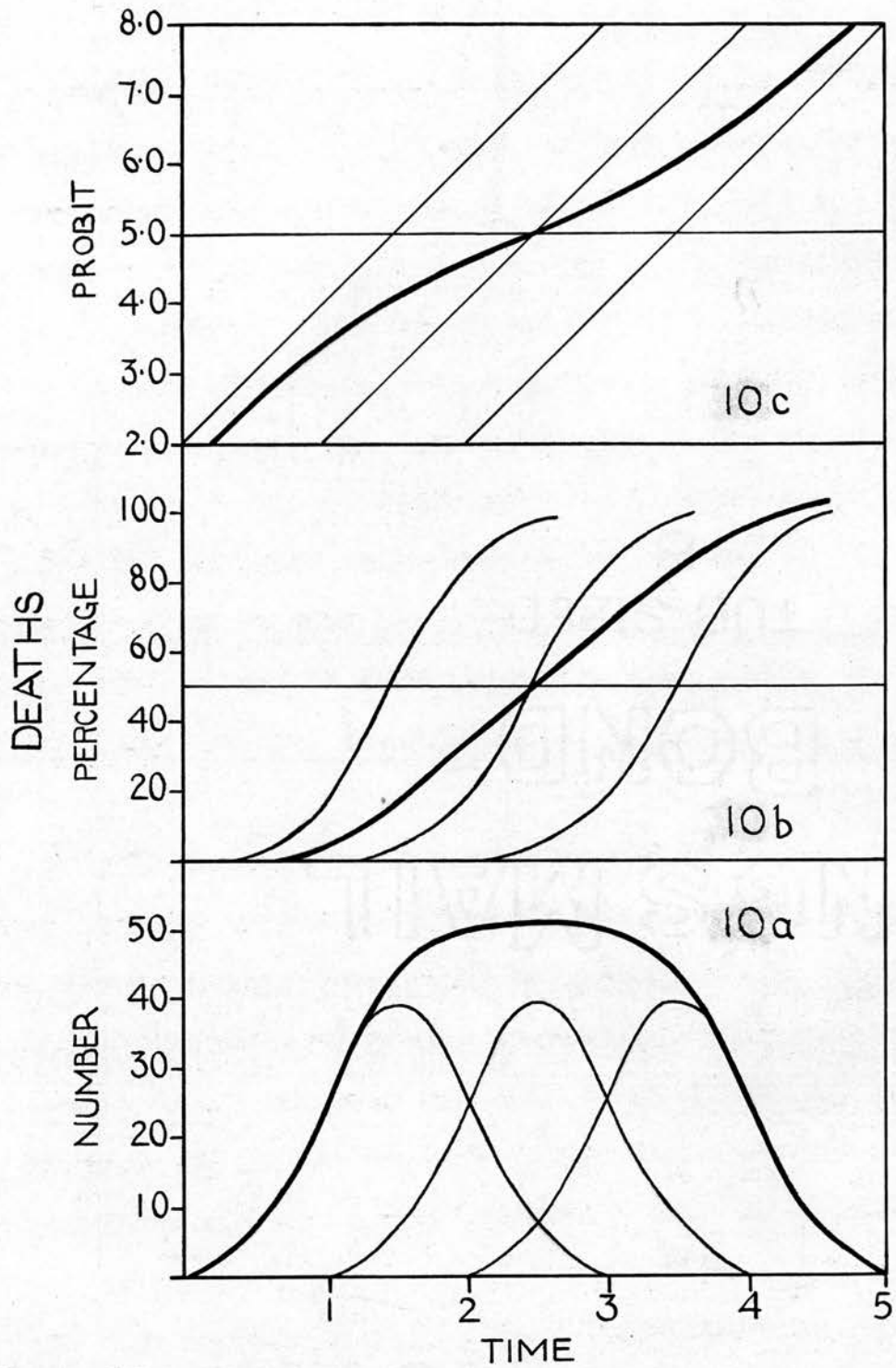

Figure 10. Distributions of times of Deaths after Diagnosis of Groups of Patients bearing Cancers of three closely related Degrees of Malignancy, and Combined Distribution of Times of Deaths of all Patients.

Thin Lines = three constituent distributions.
Thick Line = combined distribution.
a. = frequency distributions.
b. = cumulative percentage distributions.
c. = probit transformation of distributions.

Logarithmic Time Scale.

(NOTE: Scale of ordinate different in each Graph.)

(It is assumed that the three distributions have equal numbers and the same S.D.) When the times of dying of all the individuals in all the series are presented as a single frequency distribution, the resulting distribution is one with its hump flattened. When this combined distribution is transformed it takes the form of a curve of reversed sigmoid shape which runs first to the more malignant side of the central distribution then crosses over it at the 50% death level, and then turns again and runs on the less malignant side of the central degree slowly converging to the line of the least malignant degree.

Owing to the crudeness of our method of assessing malignancy, the stage distributions in practice will include cancers of different degrees of malignancy and will therefore rarely be strictly "normal". The points at which, and the acuteness with which, the "cross over" occurs will depend on the relative numbers in each distribution and how widely divergent the means of the individual distributions are. Provided the majority of patients have cancers of uniform malignancy then the "cross over" will occur beyond the mean lethal time which will be little affected in the graphical estimate of the mean.

(With a range of malignancies which lie close together, if each malignancy is represented by the appropriate number of patients then the combined distribution may be approximately normal in type and the probit line becomes almost entirely "cross over". The combined distribution of Stages A, B, C_1, & C_2 of rectal cancer patients - "total" distribution in Table V - is approximately normal and transformation produces a nearly straight line.)

(Minor degrees of a reversed sigmoid type of curve in a cumulative log. time distribution curve are not uncommonly obtained with experimental animals which have all received the same dose of drug. This is due to inclusion of subgroups of animals which have similar genetic constitution.)

3. We have assumed that if we followed our patients long enough the distributions would be completed and all the patients die of cancer. At the less malignant degrees of some cancer sites however, some patients would live to die a non-cancer death. Cases of neoplastic growth that are histologically on the border line of "malignancy" may or may not metastasise during the natural term of life. But those that died of cancer would probably form the lower part of a normal distribution.

As in animal experiments, a dose may not be large enough to kill all the animals but those that do die have survival times which form the lower end of a normal distribution.

Accordingly, for practical or natural reasons, the distributions will be "truncated". The procedure for obtaining the best fitting line to represent these distributions is similar to that given previously. The difference is that a provisional line is drawn first through those points which are distributed normally. Those points (if any) at the upper end which deviate systematically from this distribution are discarded and a regression line through the remaining suitable points is fitted by eye or by calculation.

The estimates of the mean and standard deviation are obtained as before from the graph. These will not be as accurate of course, as those calculated from the entire distribution.

For this reason when tests of significance are applied the standard error of the mean (log.) has to be corrected by multiplying it by a constant, the value of which depends on the point at which the distribution has been truncated. This constant E can be obtained from Table VIII of Bliss, (1937).

The greater the degree of truncation the less accurate is the standard deviation from the graph, and the greater the constant E must be to increase the estimate of standard error of the mean. Provided the truncated portion of the distribution is not more than 25% of the total observations, then the correction factor is so close to 1 that for ordinary medical purposes the uncorrected estimate of the standard error is probably adequate.

In cancer treatment the distributions might also be irregular at the lower end since operative interference might result in premature deaths. In fitting the regression line, it might be advisable to ignore that part of the line formed by the points representing the deaths in, say, the first 2 or 4 weeks. Even if most of the distribution is available, it would generally be wiser to use that portion of the curve representing between 16% - 84% of the deaths, i.e. between - 1 S.D. and + 1 S.D., or between 4 and 6 probits. (Operative deaths however must be included in the figures for the numerator and denominator in calculating percentage deaths.)

Test of Significance. By using the methods outlined above, it is possible for tests of significance to be applied and the number of patients required to show one distribution or regression line

FIGURE 11.

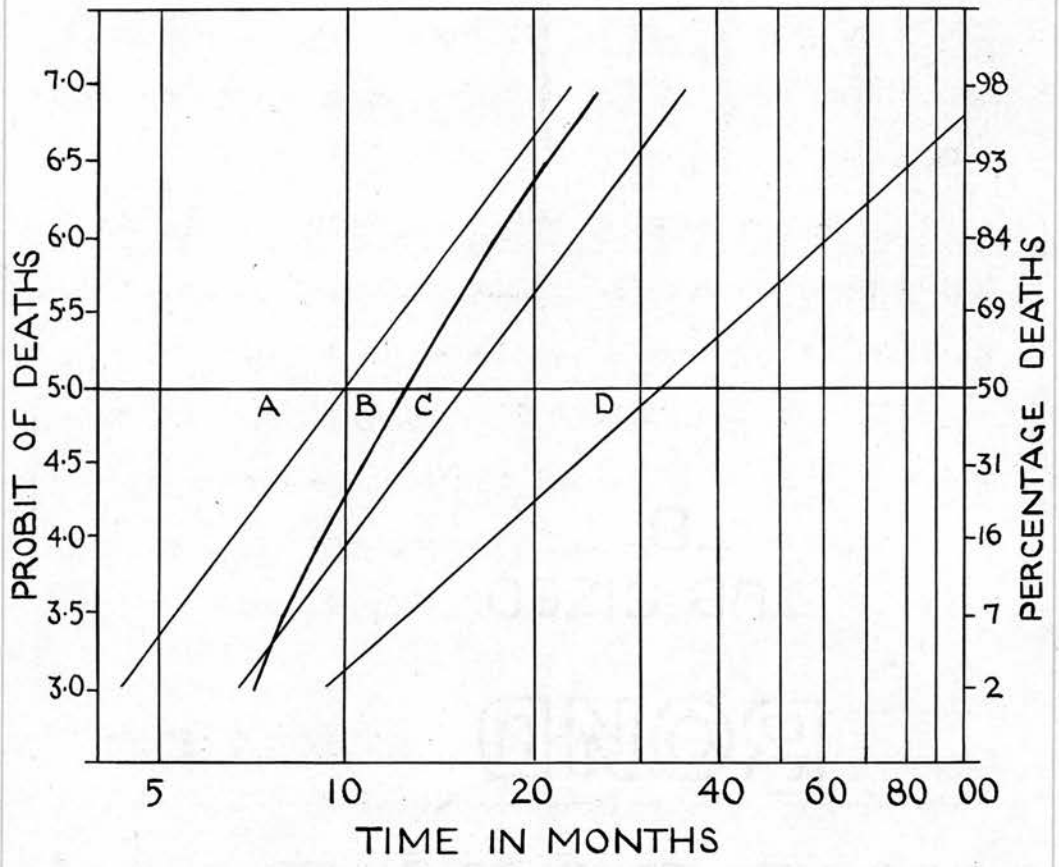

Figure 11. Probit Transformation of Distribution of Deaths of a Group of Untreated Cancer Patients: and Distributions of the Same Patients after the Time of Survival of Each Patient has been increased in certain Proportions.

Logarithmic Time Scale.

A = Original distribution.

B = Distribution after prolongation of the life of each patient by a constant time irrespective of time of survival without treatment.

C = Distribution after prolongation of each life by a constant logarithmic time irrespective of time of survival without treatment.

D = Distribution after prolongation of each life by a constant proportion of the logarithmic time of survival without treatment.

as being significantly different from another is much less than if the index of cure were the five year survival rate.

If a new form of treatment were better than those now current, it might prolong the life of each patient in any one of at least four ways.

1. By a constant time irrespective of the natural time of survival without treatment.

2a. By a constant proportion of the absolute time he would have survived without treatment, or what is the same

2b. by a constant log. time irrespective of time of survival without treatment.

3. By a constant proportion of the logarithm of the time he would have survived without treatment.

The theoretical distributions of times of dying and the probit transformations of a population whose individual survival times were increased by each of these three methods is shown in Figure 11.

Improved treatment will be shown by a shift of the site of the line to the right and possibly by a change in its slope. It is most likely that method two will, in fact, be the one found to result- increase in the mean lethal time with no change in the standard deviation. The line of the distribution

of deaths after improved treatment will then be parallel to the line of distribution of deaths after the old treatment.

4. The Extension of the Method to make use of Other Factors.

The Use of other Attributes. So far, extent of spread at diagnosis has been used as the most accurate single criterion of degree of malignancy in the rectum. But there are other sites, e.g. thyroid, in which measurement of extent of spread is not possible - at least it is not easy to classify tumours into stages. It would then be necessary to fall back on some other attribute; in the case of the thyroid the histological pattern is generally a fair guide to prognosis and length of survival.

Use of Multiple Attributes. There is no need to confine ourselves to one attribute - in fact it is undesirable since we are ignoring useful information which might help to predict cancer behaviour more clearly. Any characteristic of the tumour or the patient which can be measured however crudely should be noted.

We can thus define a subgroup by two or more attributes. Each of our "extent of spread" stages of rectal cancer could be subdivided into four

FIGURE 12.

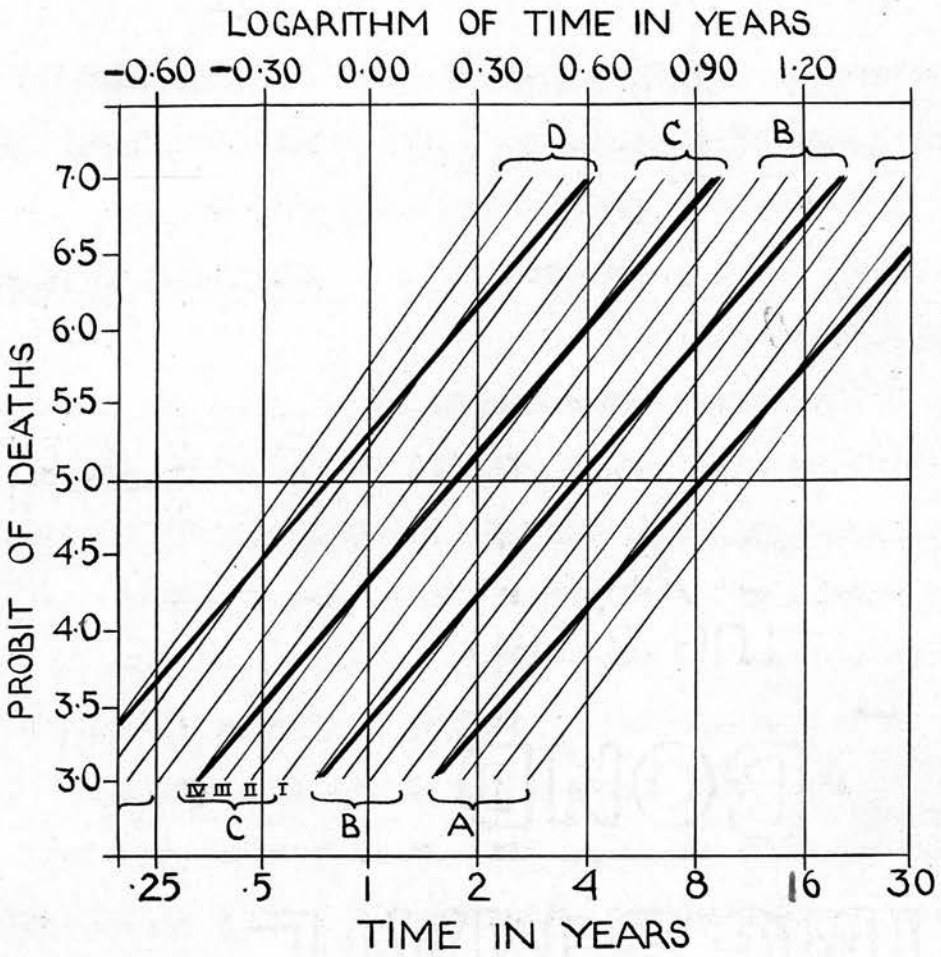

Figure 12. Diminution of Standard Deviation of Distribution by use of a Second Attribute to classify Cancer Patients.

Thick Lines = Distribution of deaths of extent of spread stages A,B,C, and D, of cancer at some site.

Thin Lines = Distribution of deaths of subclasses resulting from division of each extent of spread stage group into four subgroups which are classified by histological grade I, II, III or IV.

subgroups, each subgroup classified by an histological grade of malignancy. (It would have been better if histological grading had been divided into 3 or 5 grades.) We would then have 20 subgroups in place of 5 main groups.

The linear transformations of each of these subgroups can then be plotted and provided histological grade of malignancy is associated with prognosis we should get straighter lines than those of the main groups. (Dukes (1940) claims that such an association exists.) It has been pointed out before, that the slope of the line formed from a distribution which is the sum of several smaller closely related but slightly dissimilar distributions is always less than each of the individual distributions. That is, the variance of the summed distribution is probably always greater than the variance of any one constituent distribution. This can be shown graphically in Figure 12. The thick lines represent the probit transformation of distributions of times of dying or extent of spread stages of an imaginary series of cancer patients. The thin lines represent the distributions of the subgroups into which these main groups might have been divided by the use of histological grading. Prognosis of an

individual case can be more accurately predicted by the use of the second attribute. Using only extent of spread as our criterion we might say that the mean lethal log. time in years of all Stage C cancers is 0.24 and the standard deviation is 0.39. But for a cancer of Stage C with an histological pattern Grade III the mean lethal log. time is 0.19 and the standard deviation is 0.32. The subgroups could again be subdivided a second time by a third attribute. Provided each characteristic of the tumour is associated with malignancy and killing power the more attributes by which the tumour is classified the more nearly vertical becomes the probit transformation of the distribution of each subgroup of tumours which have the same characteristics. That is the standard deviation diminishes. The characteristics of the patient as well should be used e.g. sex, age, state of nutrition, site of tumour, time from first symptom to treatment, etc.

The significance of each factor in influencing the time of survival can be calculated mathematically. Equally important tests of significance can be applied between one series of patients and another by the use of the multiple regression equations, and the calculation of the standard error of the estimate of the

mean of the regression lines of the two series. This is a problem of considerable mathematical complexity.

A very much simpler method is to perform a "t" test using the means of each subgroup. The means are arranged in a two way table and the probability of finding by chance such differences between the mean values for each subgroup in the two series can be calculated and the significance of such differences can be assessed.

5. Some Difficulties.

If a form of treatment were introduced which absolutely "cured" some patients and had no effect on others, then those that died might not necessarily form part of a "normal" distribution and the method suggested here would not be applicable. Such a treatment however, would almost certainly prolong the life of those not "cured" and the distribution would then become a "biologically truncated" normal distribution. If a "curative" treatment were introduced it would be obviously so and there would be no need for statistical analysis to prove it. (Compare penicillin in pneumonia with the serum treatment of pneumonia.)

If patients who do not have cancer at all are included among those labelled "cancer" we may get a distribution of deaths which is not normal. It is often difficult to make the diagnosis or exclude the diagnosis of cancer merely by histological examination of the excised organ. Overdiagnosis of prostatic carcinoma, even by the most experienced surgical pathologist, probably accounts for 5 - 10% of the total cases labelled prostatic carcinoma. The time distribution of deaths of the supposed cancer patients will be a combination of the two widely differing distributions, that of patients with cancer and that of patients with simple prostatic hyperplasia. If the latter form an appreciable proportion of the total, then the probit transformation results in a curve which is far from a straight line (as curve B in Figure 15). The patients who die of cancer may in themselves form part of a normal distribution but the denominator of the proportion from which the probit percentages are derived is larger than it should be.

The Use of the Mode. One possible way out of the difficulty is to use the mode as the average measure in place of the mean or the median. In a normal distribution, mode = mean = median.

FIGURE 13.

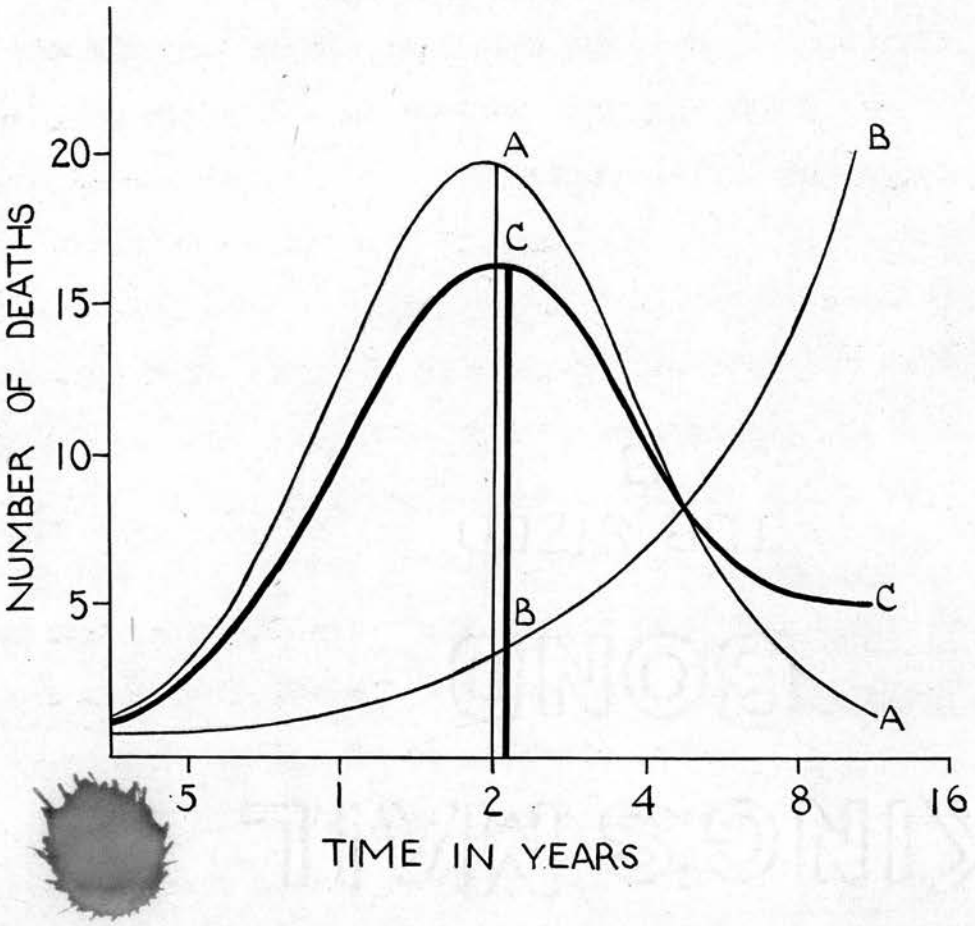

Figure 13. Use of Modal Time of Dying to estimate the Number of "True" Cancer Patients in a Series of Patients labelled Prostatic Carcinoma but actually containing an Unknown Number of Non-Cancer Patients.

Logarithmic Time Scale.

A = Frequency distribution of times of dying of "true" cancer patients.

B = Frequency distribution of times of dying of non-cancer patients.

C = Frequency distribution of times of dying of a series of patients of which 80% were "true" cancer patients and 20% were non-cancer patients.

All three distributions contain equal numbers.

If we plot a frequency polygon with the abscissa measured in log. time units then the mid-point of the interval of time in which the greatest number of deaths occurs will be an estimate of the modal log. time of dying of the cancer patients (= mean log. time theoretically). The accuracy of this estimate will depend on the size of the sample and the fineness of the grouping the data will permit. The two individual distributions of dying - "true" cancer patients and non cancer patients - can be represented in Figure 13. The distribution in the heavy black line shows a distribution composed of 80% of cancer patients and 20% of non-cancer patients. The modal log. time of dying of the combined distributions differs little from the mean log. time of the true cancer patients. That part of the curve lying to the left of the modal time will then represent roughly the lower half of the distribution of "true" cancers. A probit transformation of the lower part of the distribution of true cancers can be constructed and estimates of the mean and standard deviation obtained.

It may be that the crude modal lethal time would be difficult to calculate because the number of patients is small and the grouping coarse. Possible

solutions of the difficulty are:-

1. Assuming we are dealing with the lower half or two thirds of a normal distribution it is possible to calculate the constants of the distribution (mean and standard deviation) even although the number of individuals in the truncated portion is unknown. The mathematical calculations involved require professional mathematical skill.

2. A reasonably accurate solution could probably be obtained graphically. A frequency polygon is constructed and an estimate of the mode, however crude, is made.

The number of deaths lying to the left of the mode is doubled and taken as the total "true" cancer patients. The probit transformation of the distribution of deaths is calculated with this number as the denominator for calculation of the proportion of deaths up to the end of each time interval, and a provisional curve drawn up. If this is not a reasonably straight line then the denominator is increased or diminished by, say 10% and a further provisional curve obtained; continue to vary the denominator for the calculation of the percentage dying, until the points of the probit distribution lie with lower half or 2/3rds of the distribution as

FIGURE 14.

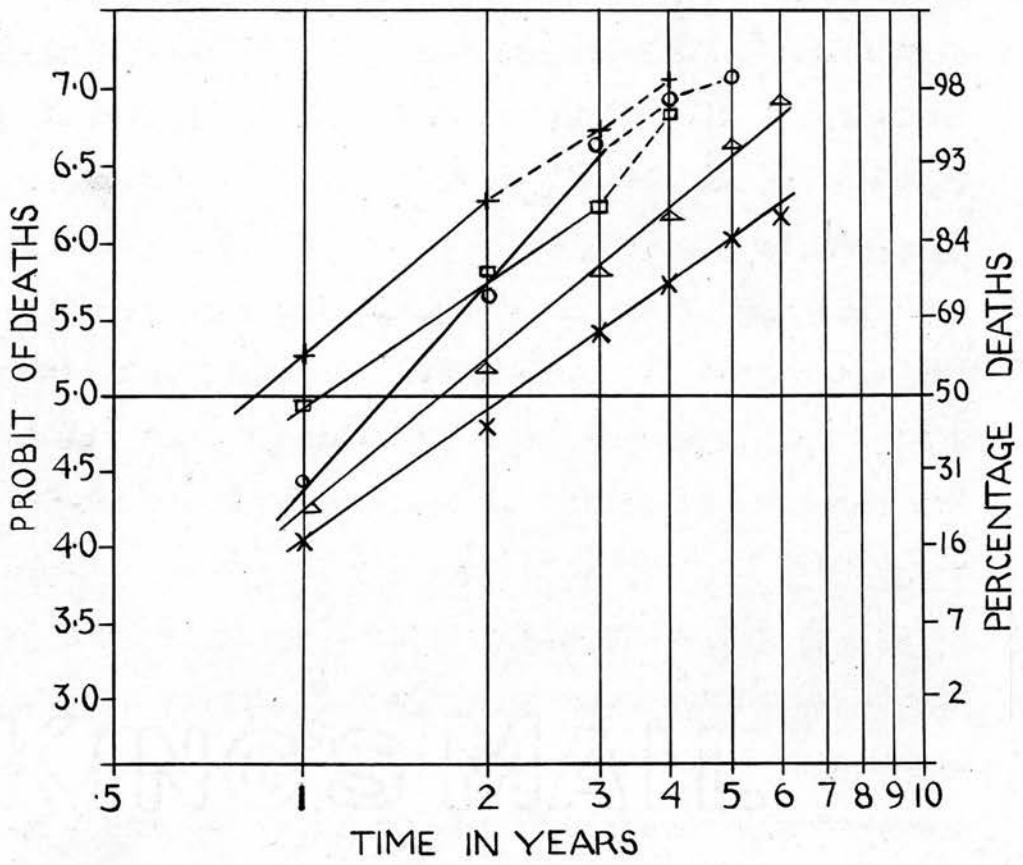

Figure 14. Probit Transformations of Distributions of Deaths of Patients with Untreated Cancer at various Sites, Greenwood's Data (1926).

✕——✕ = Cancer of Breast.

△——△ = Cancer of Rectum.

⊙——⊙ = Cancer of Cervix.

□——□ = Cancer of Stomach.

+——+ = Cancer of Oesophagus.

close to a straight line as possible. This is assumed to be the distribution of the "true" cancer patients. (The final approximations can be calculated by rather complicated formulae, see Stevens in Appendix to Bliss, 1937.)

The use of the provisional estimate of mode depends on the assumption that the two distributions, cancer and non-cancer are significantly far apart. If, however, no method of staging the cancer into even crude degrees of malignancy is available, and if a wide range of degrees of malignancy exists in the particular tumour type, then it may be that the non-cancer patients cannot be separated, since the combined distribution of deaths of cancer and non-cancer might be approximately normal.

6. Lack of Proof of Cure.

In Figure 14 are seen the linear transformations of distributions of times of dying of patients with cancer at several sites who were not subjected to treatment (Greenwood, 1926). The Figure is included to show that the survivors (untreated) for five years of those cancer types which are claimed to be "curable" if "caught in time" - breast, rectum - merely represent the tail end of a distribution whose

pattern could have been predicted with an high degree of accuracy at the end of the first year after diagnosis. In the less malignant groups of cancers at these sites, even when untreated, the proportion of the distribution lying to the right of the five year ordinate would be expected to be much greater merely as the result of chance variability in behaviour.

A substantial proportion of the patients who bear the less malignant cancers and who survive for five years after treatment would have survived for five years without it. It is suggested that most of the so-called "cures" resulting from treatment are contributed by this proportion.

We have suggested earlier that the principal factor influencing survival after treatment is the inherent malignancy or "cancerousness" of the tumour. A study of these regression lines supports the argument that treatment is merely palliative.

Suppose there are 100 cancers of Stage C1 at the start. 41 of these survive for five years and will be claimed as "cured". This number should represent; 1. those patients whose cancer has been successfully removed, less a small number who have died a non-cancer death in the first five years; 2. those odd

TABLE VII.

EXPECTED RATE OF DYING IF CANCER WERE CURABLE.

Years after Diagnosis	Expected % Deaths in Uncured	Expected Number of Deaths in 57 Uncured	Expected % Deaths in Cured	Expected Number of Deaths in 43 Cured	Total Number of Deaths Expected
0.5	4	2	1	0	2
1	24	14	2	1	15
2	57	32	4	2	34
3	79	45	6	3	48
4	89	51	8	4	55
5	95	54	11	5	59
6	97	55	14	6	61
7	99	56	17	7	63

Table VII. Number of Deaths expected to occur by the End of each Year in 100 Cancer Patients with Stage C_1 Cancer of Rectum.

Figures are based on the assumption that 57 "uncured" cancer patients should behave like untreated cancer patients (as in Figure 15) and 43 "cured" patients should behave like a control population which did not have cancer.

FIGURE 15.

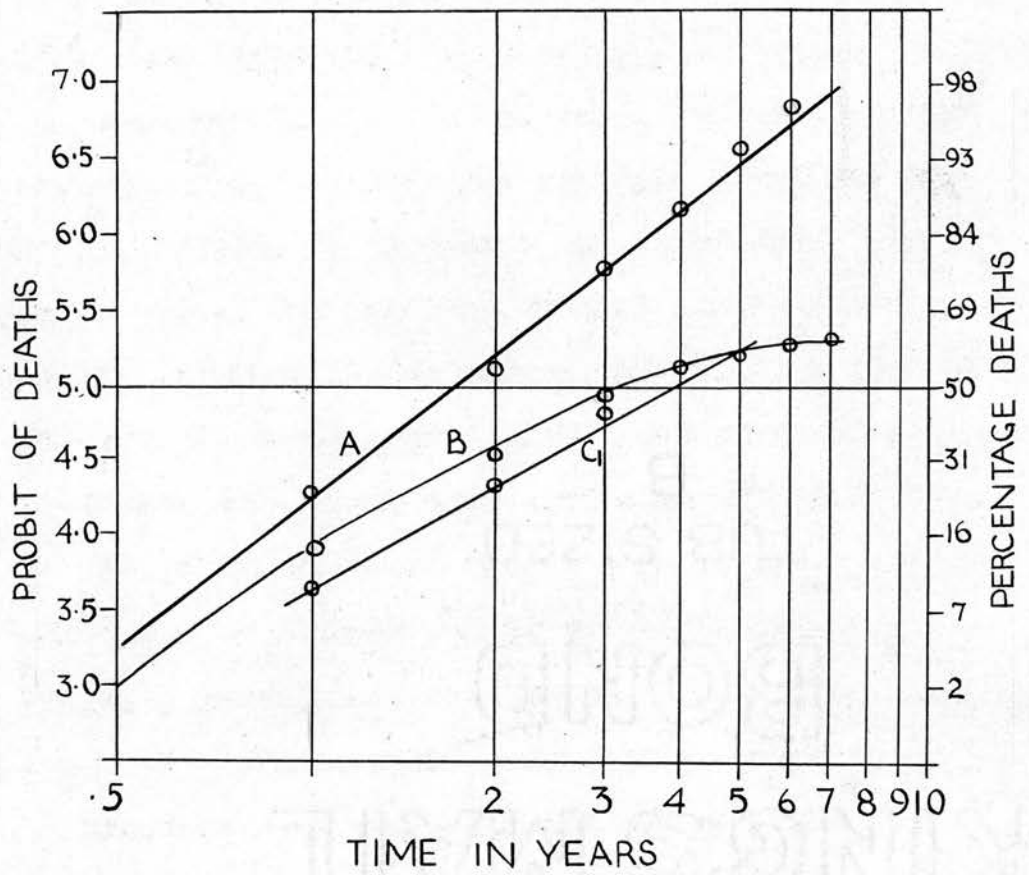

Figure 15. Probit Transformation of Expected Distribution of Deaths of Stage C_1 Cancers of Rectum if Cancer were "Curable".

Logarithmic Time Scale.

A = Distribution of untreated rectal cancer patients.

B = Distribution of deaths of an imaginary series of C_1 rectal cancer patients, of which 57% were "uncured" and behaved like untreated rectal cancer patients and 43% were "cured" and behaved like controls. Data as in Table VII.

C_1 = Distribution of deaths of C_1 cancer patients, as actually observed.

patients in whom treatment has failed but who have just managed to survive beyond the five year limit. Assume therefore there are 57 patients in whom treatment has failed and who will behave like untreated cancer patients. The remaining 43 will behave like a control population who have not got cancer at all. If this were so then deaths should occur in the 100 patients as in Table VII. When these figures are plotted either as a log. time-cumulative frequency distribution or as a linear transformation, the distribution of deaths is not normal. In the latter case the line is a curve with diminishing gradient after a sharp initial rise (Figure 15). The line "tails off" for the reasons given in a previous section but in this case the two populations (cured and uncured) have widely divergent means and not closely related as before.

Since the members of this imaginary series are not dying off according to the expected behaviour of untreated cancer, then the diminishing gradient, i.e. diminished rate of dying, could justifiably be ascribed to treatment. (The probit lines of Greenwood's untreated cancers and Duke's Stage C_1 cancers are given for comparison.)

In actual fact, none of the lines representing

stage groups of rectal cancer patients does "flatten out" to this extent (at least not the most malignant groups). Each group forms a sample of a normally distributed population still "normally distributed" even after treatment. Treatment appears to prolong life by only a small proportion (not necessarily arithmetic) of the time patients would have survived without treatment.

The great attraction of dividing cancers into stages is that it allows the surgeon or radiotherapist to deceive himself into believing that he has achieved a high rate of success in at least some group of cancers, - the least malignant ones.

7. Checking the Consistency of the Diagnoses.

A study of the total distribution of deaths after diagnosis and treatment at any site shows that these distributions are of normal type. It has also been shown earlier that the distribution of deaths at each degree of malignancy was also normal. The only way in which these conditions can arise is when the numbers of the individuals constituting each degree of malignancy are also normally distributed. We are therefore entitled to propose the general law that:- "At any site the frequencies of occurrence of cancers

at the individual degrees of malignancy are normally distributed."

If we wish to test the accuracy of diagnosis in a series of cancer patients which is presented after having been submitted to a new form of treatment there are at least two methods.

1. The distribution of deaths from the whole series is plotted (including untreated cases). If the mean and standard deviation derived from the lower half of the distribution do not show a significant difference from those of previous forms of treatment then any superiority claimed is likely to be due to inclusion of cases which were not malignant or of a greater proportion of cases which were of a lower degree of malignancy than the average. This will be confirmed if the line "falls away" and takes the form of the line B in Figure 15. The more closely the points of the distribution fit a straight line the more accurate is the diagnosis likely to be.

When the distributions at each stage or degree are then contrasted, if the differences are only observed in the least malignant degree or degrees, then it is almost certain that the standard of diagnosis was not the same in the two series.

2. When a series of cancers are divided by

"stages" or by some other assessment of degree of malignancy then the numbers in each stage group should be such that the central degrees of malignancy contain an higher proportion of the total than either the higher or lower degrees of malignancy, i.e. that the numbers in the degrees be roughly normally distributed. If the least malignant degree of the test series contains an higher proportion of cases than the control series then any apparent superiority of treatment in the test series is likely to be due to the preponderance of cancers of lower degree. We could perform a χ^2 test on the numbers in each group of the two series and find if they were likely to have been drawn from the same population. If there is a significant difference then there has probably been bias in the allocation of the cases.

A claim for an increase in the overall cure rate of cancer at some site should be viewed with suspicion if the proportion of "early" cancers in the lower degrees of malignancy in the series presented is greater than is usually found.

These tests assume that in any geographical area of reasonable size in Great Britain the cancers which occur at any one site are not, as a group, likely to differ materially with respect to age,

duration of symptoms, etc., at the time of diagnosis from those occurring in adjacent areas.

VII. DISCUSSION and SUMMARY.

It is generally realised that the five years survival rate is not a satisfactory measure of the value of cancer treatment but it continues to be used because there is thought to be nothing better.

The treatment of cancer, especially by radiotherapy, is expensive, yet at few cancer sites is there general agreement as to what is the best form of treatment. Present methods of treating cancer are the same as they were 25 years ago. If present methods of analysing the end results of treatment have not shown one or other form of treatment to be the best, then either the methods of analysis are inadequate or all treatments are equally effective or ineffective.

It is surprising that the World Health Organisation Sub-Committee on Registration of Cases of Cancer should report - "(a) The absence of any commonly agreed method of calculating survival and apparent recovery ("cure") rates for cancer leads to great confusion and prevents correct comparisons of the results of different therapeutic procedures." and then recommend that the method usually used at present - percentage survival at the end of each year - is the method of choice. Admittedly, the

details of the method suggested are clearly defined but essentially similar and probably equally efficient methods have been in use in many centres for years without diminution of the "confusion" in these centres.

It is not appreciated that the principal source of the "confusion" is, not in the method of analysis of the figures themselves, but what is included in the counting. Surgeons and radiotherapists do not realise, or ignore, that the diagnosis of cancer at the time when the diagnosis is made, is merely skilled guessing. There is little doubt that most, if not all "better" treatments, depend for their apparent superiority on the employment of an histologist with less rigid criteria of malignancy than the average, or on the failure to employ an histologist at all.

On reading elaborate collections of the end results of cancer treatment, one gets the impression that the editors believe that if they could get more and more series of five year survival rates then they would get closer to the truth and be able to prove that this or that treatment is best. This is unlikely. In each series we do not know the number of wrongly diagnosed cases and the relative

malignancies of the individual cancers. Since in cancer there is a bias to overdiagnosis, the errors in clinical or histological judgment do not cancel one another out and comparisons between the averages of groups of series are not likely to be much more valid than between individual series.

The source of all the fallacies is that today we have no accurate single measure of the degree of "cancerousness" of any neoplasm at the time of diagnosis. In order to minimise the effects of errors in diagnosis it is suggested firstly that, paradoxically, the numbers dying should be the basis of our index of "curability" since if the patient dies of cancer there is little doubt the diagnosis was correct; secondly, since our measure of cancerousness is so crude, we should direct our attention in each group of patients with cancers which we believe to be of the same stage or degree of malignancy, to that half or portion of the group which dies most rapidly. These patients presumably bear a high proportion of the more malignant tumours of that stage or degree and their tumours are accordingly more uniform in their "cancerousness".

It is suggested that, for everyday clinical use, the Median Lethal Time after diagnosis is a simpler

and more accurate index than the five year survival rate.

It has been postulated and is generally demonstrable that, if time is recorded on a logarithmic scale, then the frequencies of the times of survival after diagnosis of individual patients with cancers of the same degree of malignancy are normally distributed. We find that the more rapidly dying half or two thirds of our patients in each stage form the lower part of an approximately normal distribution. Since the distribution of deaths is assumed "normal" then theoretically, the median = the mode = the mean. If we obtain an estimate of the mean log. time and its standard deviation, the distribution of our times of dying is defined and it is possible to apply tests of significance for differences between comparable series. Under certain circumstances it might be more accurate to employ the mode and assume this equals the mean.

A statistician could determine an accurate estimate of the mean log. time of survival for a particular stage or type of cancer. Experience would show that unless a new form of treatment increased the median lethal time by a certain proportion of the standard for the region, then further

mathematical analysis would be unlikely to show the difference as significant.

By extension of this method to include the study of the influence of multiple characteristics in either the patient or the tumour an intricate system of analysis can be built up. Although for full accuracy the mathematical procedure of the analysis of variance is complex, fairly accurate results can be obtained by simple graphical methods.

The methods outlined here were intended to be applied to the study of the behaviour of human cancer in the hope of accurately measuring the importance of any factor, in the tumour or the host, which might influence the period of survival. The measurement of the possible influence of treatment has here been given pride of place but the methods need not be confined to the analysis of this factor alone. It is likely that treatment does not greatly influence the subsequent course of the majority of cancers.

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